- The patient was removed from the study and placed on alternate antibiotic therapy because of persistent, worsened or new signs and symptoms of acute infection.

UNABLE TO DETERMINE:

- No post-treatment evaluation of signs and symptoms was done (i.e., no Test of Cure Visit); or
- The patient received another systemic antibiotic with documented (i.e., in the package insert) activity against the pre-treatment pathogen, for an infection other than bronchitis, prior to the TOC visit; or
- The patient did not receive a minimum of 3 days of therapy.

***Bacteriologic Response***

Each pre-treatment pathogen was assigned a bacteriologic response of Eradicated, Presumed Eradicated, Persisted, Presumed Persisted or Unable to Determine:

ERADICATED:

- The original pathogen was absent from the culture of a good quality sputum specimen (i.e., >25 PMN per LPF and < 10 epi per LPF) obtained at the TOC visit.

PRESUMED ERADICATED:

- The patient was not producing sputum (i.e., there was no source to culture) at the TOC visit and the clinical response was Cured or Improved.

PERSISTED:

- The original pathogen was present in the culture of a good quality sputum specimen (i.e., >25 PMN per LPF and < 10 epi per LPF) obtained at the TOC visit .

PRESUMED PERSISTED:

- The patient was not producing sputum (i.e., there was no source to culture) at the TOC visit and the clinical response was Unsatisfactory.

UNABLE TO DETERMINE:

- No post-treatment evaluation was done (i.e., no TOC visit); or
- The patient received another systemic antibiotic with documented (i.e., in the package insert) activity against the pre-treatment pathogen, for an infection other than bronchitis, prior to the TOC visit; or
- The patient did not receive a minimum of 3 days of therapy; or
- The patient's pre-treatment pathogen was resistant to gatifloxacin.

*Relapse*

Patients who had a clinical response of Cured at the time of the Test of Cure visit were evaluated for relapse at the extended follow-up assessment (Day +21 to Day +28). Relapse was defined as:

- Worsening, or recurrence after initial improvement/resolution, of the signs and symptoms related to the acute infection (cough, dyspnea, sputum production, sputum purulence); or
- Appearance of new clinical signs and symptoms of acute respiratory infection without documentation of a new pathogen; or
- Persistence, worsening or emergence of new signs and symptoms of acute bronchial infection requiring alternate antibiotic therapy.

Pathogens isolated from relapsed patients were speciated and tested for susceptibility to gatifloxacin and other antibiotics as appropriate.

*New Infections*

- Isolation of a new pathogen from a purulent sputum specimen in the presence of signs and symptoms of AECB;
- Isolation of any pathogen from a new site of infection, with associated clinical signs and symptoms;
- The presence of clinical signs and symptoms indicative of a new infection for which a culture would not usually be obtained (e.g., skin infection).

Pathogens isolated from patients with new infections were speciated and tested for susceptibility to gatifloxacin and other antibiotics as appropriate.

Safety variables and deaths were collected between the first day of study drug treatment and 30 days after the last day of study drug treatment, inclusive.

*Adverse Clinical Events*

Investigators reported all adverse clinical events to the Sponsor, along with their judgment of the causality. For the purpose of analysis, events that were certainly, probably or possibly drug-related were grouped and categorized as "drug-related". Investigators also assessed the severity (mild, moderate, severe, or very severe) of each adverse clinical event.

*Abnormal Laboratory Results*

Any worsening in laboratory parameters during or post-treatment was categorized according to a severity grading scale derived from the National Cancer Institute's Common Toxicity Criteria (CTC) or the Acquired Immune Deficiency Syndrome (AIDS) Clinical Trials Group (ACTG) classification of laboratory abnormalities. Four grades of

abnormality were defined (Grades 1-4), and the range of laboratory values associated with each grade was established for each test.

***Reviewer's comments:*** *Clinical, microbiologic and laboratory endpoints were adequately and accurately defined prior to study initiation.*

## 8.2.1.3.3 Statistical Considerations

*Data Set Descriptions*

There were four study populations of interest:

- All Treated Patients: All patients who received at least one dose of gatifloxacin.
- Eligible Patients: All Treated Patients with a diagnosis of AECB at entry, defined as:
  - Having evidence of purulence in an adequate pre-treatment sputum sample (>25 PMN per LPF – the original inclusion criterion required <10 epithelial cells as well, but this criterion was relaxed as previously stated).
  - Having two or more of the following signs/symptoms of AECB:
    - increased dyspnea/cough;
    - increased sputum production;
    - increased sputum purulence.
  - Having a pre-treatment radiograph that did not show pneumonia.
- Clinically Evaluable Patients: All Eligible Patients who:
  - Had a duration of dosing of at least five days (with the exception of early treatment failures) and received at least 80% of the planned doses for the dosing duration;
  - Had a post-treatment clinical assessment within the Day +5 to Day +18 window for the Test of Cure visit (except for failures); and
  - Did not receive a systemic antibacterial agent between the time of the pre-treatment visit and the post-treatment assessment.
- Microbiologically Evaluable Patients: All Clinically Evaluable Patients who:
  - Had at least one pre-treatment pathogen that was gatifloxacin non-resistant (i.e., either fully or intermediately susceptible); and
  - Had a culture performed on a purulent sputum specimen, or were unable to produce sputum, at the Test of Cure Visit.

***Reviewer's comments:*** *The 4 datasets are adequate and, except for the Test of Cure window and the relaxation of the sputum criterion, correspond to prospective definitions the sponsor and FDA had agreed upon.*

*Statistical Analyses*

Analyses of the pre-treatment characteristics for All Treated, Eligible and Clinically Evaluable Patients were performed. Prognostic factors were also summarized. Treatment parameters were summarized for All Treated, Clinically Evaluable and Eligible Patients.

The following efficacy parameters were analyzed and presented in the body of the report:

- Clinical response rate for Clinically Evaluable and Eligible Patients;
- Satisfactory clinical response rate by prognostic factor for Clinically Evaluable Patients;
- Satisfactory clinical response rate by pathogen for pre-treatment pathogens isolated from Clinically Evaluable Patients;
- Bacteriologic eradication rate by pathogen for the gatifloxacin non-resistant principal respiratory pathogens isolated pre-treatment from Microbiologically Evaluable Patients;
- Bacteriologic eradication rate by pathogen for the principal respiratory pathogens isolated pre-treatment from Eligible Patients.

In addition, the clinical response rate, satisfactory clinical response rate by prognostic factor, satisfactory clinical response by pre-treatment pathogen, and bacteriologic eradication rate by pre-treatment pathogen were analyzed for All Treated Patients. Ninety-five percent confidence intervals were constructed around the satisfactory clinical response and clinical cure rates for Clinically Evaluable, Eligible and All Treated Patients using an exact method (StatXact-3®).

*Safety*

All patients who received at least one dose of gatifloxacin were evaluated for safety. The frequencies of adverse clinical events were summarized by relationship to gatifloxacin and displayed by primary term within the relevant body system, as defined in the COSTART adverse clinical events classification system, which was modified by the applicant. Those adverse events that were considered by the Investigator to be drug-related (i.e., certainly, probably or possibly drug-related) were also tabulated by severity.

Changes in laboratory test results were tabulated by test. For patients with normal (Grade 0) pre-treatment laboratory test values, the frequencies of Grade 1, 2, 3, and 4 abnormalities during/post-treatment were displayed. For each patient, the most abnormal result for each test was counted. For patients with abnormal (Grades 1, 2, or 3) pre-treatment laboratory test values, the frequencies of worsening to Grade 2, 3, or 4 abnormalities during/post-treatment were displayed. For each patient, the worst grade change for each test was counted.

## 8.2.1.4 Results

### 8.2.1.4.1 Populations

The first patient was enrolled on February 6, 1997. The last visit by the last patient enrolled was on May 23, 1997. A total of 210 patients were enrolled in the study; all received at least one dose of gatifloxacin.

Significant protocol violations were defined as those that prevented a patient from being clinically evaluable. Forty-eight major protocol violations occurred (Table 2).

Table 2 Significant Protocol Violations

| Violation | Number of Patients |
|---|---|
| Any | 48 |
| No purulent sputum specimen pre-treatment | 31 |
| No post-treatment evaluation | 12 |
| Minimum dosing requirement not met | 3 |
| Evidence of pneumonia on pre-treatment x-ray | 1 |
| Received another antibiotic before the post-treatment evaluation[a] | 1 |

[a] For an infection unrelated to the current episode of AECB.

Of 31 patients who did not have a purulent sputum specimen pre-treatment, 27 were allowed to enroll at a single site based on preliminary reading of the sputum Gram stain smears by site personnel. These preliminary readings were not corroborated by the laboratory.

One hundred seventy-eight patients were Eligible and 162 patients were Clinically Evaluable (Table 3). One hundred one patients were Clinically and Microbiologically Evaluable. The rates of eligibility and evaluability were fairly constant across sites, although only seven of 34 patients were clinically evaluable at one site.

Table 3 Distribution of Patients in Study Populations and Reasons for Exclusion

| Study Population/Reason Excluded | Number (%) of Patients N = 210 |
|---|---|
| **Treated** | **210 (100)** |
| **Eligible** | **178 (85)** |
| **Ineligible** | **32 (15)** |
| Reason Ineligible: | |
| No Pre-treatment Purulent Sputum Specimen | 31 (15) |
| Evidence of Pneumonia on Pre-treatment X-ray | 1 (<1) |
| **Clinically Evaluable** | **162 (77)** |
| **Unevaluable** | **48 (23)** |
| Reason Unevaluable: | |
| Ineligible | 32 (15) |
| No Post-treatment Evaluation | 12 (6) |
| Insufficient Dosage | 3 (1) |
| Other Antibiotic Received | 1 (<1) |
| **Microbiologically Evaluable** | **101 (48)** |
| **Unevaluable** | **109 (52)** |
| Reason Unevaluable: | |
| No Pre-treatment Pathogen | 87 (41) |
| Clinically Unevaluable | 20 (10) |
| Gatifloxacin-resistant Pre-treatment Pathogen | 2 (<1) |

***Reviewer's comments:*** *Reviewer agrees with the applicant regarding the ineligibility of 32 patients whose sputum was not purulent (31 patients) or who had evidence of pneumonia on the chest X-ray (1 patient). Of 31 patients who did not have purulent sputum, 27 were enrolled at a single site. These facts were well documented on the case report forms and the databases. Reviewer also agrees regarding the unevaluability of 48 patients via the case report forms and the databases.*

*Data Sets*

The safety data set consisted of All Treated Patients.
The primary data set for analysis of clinical efficacy consisted of the Clinically Evaluable Patients; the primary data set for analysis of bacteriologic efficacy consisted of the Microbiologically Evaluable Patients. The Eligible and All Treated Patients formed secondary efficacy data sets.

***Reviewer's comments:*** *The primary analysis was not done on an intent-to-treat basis; the intent-to-treat population would be more closely represented by the All Treated or the Eligible subsets. All of the above analyses will be considered by the FDA.*

***Demography and Patient Characteristics***

Of the 210 patients enrolled, half were male; the majority (70%) were white. The median age was 49 years (range: 19 - 88).

***Medical History and Presenting Conditions***

A wide variety of medical conditions were recorded. Nearly half of the patients (45%) had a history of COPD and/or emphysema, and 20% had a history of asthma. Twelve patients had a history of neoplasia, but only one had had pulmonary neoplasia. One patient had HIV disease.

***Reviewer's comments:*** *The representation of different medical conditions was adequate and reflected the picture encountered in clinical practice.*

***Microbiologic Documentation***

A total of 173 pathogens were isolated from 123 (59%) patients. Of the 123 patients, 83 (67%) had a single pathogen and 40 (33%) had multiple pathogens. There were 37 isolates of *H. influenzae*, 12 of *S. pneumoniae*, and 12 of *M. catarrhalis*. Other frequently isolated respiratory organisms included *S. aureus* (22) and *H. parainfluenzae* (12). In six of the patients from whom *S. aureus* was recovered, the sputum Gram stains were suggestive of a colonizing organism rather than a causative pathogen. All but 10 of the pre-treatment isolates were susceptible to gatifloxacin. Six *P. aeruginosa* isolates were gatifloxacin-resistant, and 3 *P. aeruginosa* isolates and one *S. maltophilia* isolate showed intermediate gatifloxacin susceptibility.

***Reviewer's comments:*** *The 3 major pathogens usually involved in AECB (H. influenzae, S. pneumoniae and M. catarrhalis) are well represented in the study. There was also a good proportion of patients with H. parainfluenzae and S. aureus to allow for assessment of efficacy against those organisms.*

***Prognostic Factors, All Treated Patients***

Most (80%) patients had Type I exacerbation; the remainder had Type II. The median duration of the current episode of exacerbation prior to enrollment was five days, and in 74% of the patients the current episode was less than eight days in duration. Twenty-five patients received concomitant systemic corticosteroids. Seventeen of these patients had been taking systemic corticosteroids chronically prior to enrollment. A patient was considered a current smoker if he or she was a smoker at the time of enrollment or had stopped smoking within the two months before enrollment. Based on this definition, 52% of the patients were current smokers, and 80% had a history of smoking.

*Study Therapy*

One hundred ninety-nine (95%) patients received 10 doses of gatifloxacin. Ten of the 11 patients who received fewer than 10 doses discontinued gatifloxacin therapy prematurely. The other patient was an early treatment failure. The duration of gatifloxacin dosing was 10 days for 197 (94%) patients, less than 10 days for 11 (5%) patients and greater than 10 days for two (<1%) patients (one patient missed one dosing day and another missed two dosing days, but both completed the full course of 10 doses in 11 and 12 days, respectively). Of 10 patients who discontinued gatifloxacin treatment, 7 discontinued it for adverse clinical events, two others did not return for the during-study visit for personal reasons unrelated to gatifloxacin therapy and could not be followed (duration of therapy based on last recorded dose), and one was removed from the study for a laboratory test abnormality at baseline identified after the start of dosing. In four of the patients who discontinued due to adverse clinical events, the events were considered by the Investigators to be gatifloxacin-related.

***Reviewer's comments:*** *The study achieved its goal of treating the majority of patients for 10 days, as 94% of them received 10 days of gatifloxacin.*

*Concomitant Antimicrobial Therapy*

Five patients received concomitant antimicrobial therapy. The three patients who received systemic medications (two antifungal, one antiviral) had initiated those therapies pre-treatment. Two other patients initiated non-systemic antifungals for adverse events that occurred during gatifloxacin treatment: one for a vaginal yeast infection (clotrimazole) and another for oral thrush (nystatin) and a vaginal yeast infection (miconazole). Gatifloxacin was not discontinued in these patients. None of the five patients were considered unevaluable for having received these antifungal/antiviral medications.

***Reviewer's comments:*** *Concomitant antimicrobials received during the study were unlikely to affect its outcome.*

*Post-treatment Antimicrobial Therapy*

Post-treatment antimicrobial agents were given to 31 (15%) patients; 26 (12%) received systemic antimicrobials and seven (3%) received non-systemic agents (two patients received one of each). The most common systemic agents used were antibacterials (23 patients).

Twelve of the 23 patients who received a post-treatment antibacterial were given an alternate antibiotic for their current episode of AECB after failing gatifloxacin treatment. Similarly, two patients who had discontinued gatifloxacin therapy prematurely due to adverse event(s) were started on an alternate antibiotic for AECB. One patient whose symptoms had improved but not resolved received antibiotic therapy on Day +19. Of the remaining eight patients, four received post-treatment antimicrobials for new infections

(one each for pneumonia and urinary tract infection (UTI); two each for sinusitis), two for relapses, and two for prophylaxis during/after elective surgery.

Other drugs of the fluoroquinolone class were given to three patients post-treatment: ciprofloxacin to one patient for sinusitis that had developed on Day +4; levofloxacin to one patient for relapse on Day +16; and levofloxacin to another patient who failed gatifloxacin therapy.

Systemic antifungal medication (fluconazole) was taken by one patient for a vaginal infection and by another for a fungal rash (therapy began pre-treatment). The patient who entered the study with HIV disease continued systemic antiviral (zidovudine) therapy begun pre-treatment. Topical antifungals were given to seven patients for vaginal infections, including one patient who also received a systemic antifungal (fluconazole) for the same infection.

**8.2.1.4.2 Efficacy Results**

## Clinically Evaluable Patients

Eighty-eight percent of the Clinically Evaluable Patients had a Satisfactory clinical response (Table 4). Seventy-one percent of the patients were assessed as Cured and 17% as Improved. None of the patients with a clinical response of Improved received a systemic antibacterial medication before the TOC visit.

Table 4 Clinical Response, Clinically Evaluable Patients

| | Number (%) of Patients | |
|---|---|---|
| Clinical Response | N = 162 | 95% Confidence Interval |
| Satisfactory | 143 (88) | (82%, 93%) |
| Cured | 115 (71) | (63%, 78%) |
| Improved | 28 (17) | |
| Unsatisfactory | 19 (12) | |

In patients with Improved clinical responses, the status of the primary signs and symptoms of AECB was evaluated at both the TOC visit and the extended follow-up visit (Day +21 to Day +28). Although many of the Improved patients had signs and symptoms assessed as improved rather than resolved at the time of the extended follow-up visit, only one patient relapsed and had to be treated with another antibiotic. All pre-treatment organisms isolated from patients with a clinical response of Improved were eradicated.

***Reviewer's comments:*** *For 5 patients at a single site, the investigator's assessment was Cured but the patients' symptoms were mistakenly entered as Improved by the investigator. The investigator later changed the symptoms response to Resolved, but this was done after the applicant's medical monitor had entered the response as*

*Improved into the database. This discrepancy was displayed by the applicant in an appendix. If those patients were to be entered as Cured, the cure rate would rise to 74% (120 out of 162) and the improvement rate would decrease to 14% (23 out of 162). The adjusted CI would be 67% - 81%, which is considered acceptable by the reviewer for the indication of AECB.*

***Clinical Response by Prognostic Factor***

The satisfactory clinical response rate for Clinically Evaluable Patients was generally similar across the categories of prognostic relevance (Table 5); no difference was noted for type of exacerbation, duration of the current episode of AECB, current smoking status, or smoking history. Systemic use of corticosteroids was the only potential prognostic indicator with a lower response rate (75% in patients with concomitant use vs. 91% in patients who did not use). The lower satisfactory response rate was primarily seen in patients with chronic corticosteroid use (12/17, 71%), compared to those who initiated corticosteroid use at the start of gatifloxacin therapy (6/7, 85%).

Table 5 Satisfactory Clinical Response Rate by Prognostic Factor, Clinically Evaluable Patients

| Prognostic Factor/Subcategory | Satisfactory Responses/Evaluable Patients (%) N = 162 |
|---|---|
| Exacerbation Type | |
| Type I | 112/126 (89) |
| Type II | 31/36 (86) |
| Duration of Current Episode[a] | |
| 7 Days | 97/109 (89) |
| >7 Days | 44/51 (86) |
| Concomitant Systemic Steroid Use | |
| Yes | 18/24 (75) |
| No | 125/138 (91) |
| Current Smoking Status | |
| Smoker | 83/93 (89) |
| Non-Smoker | 60/69 (87) |
| History of Smoking | |
| Yes | 123/138 (89) |
| No | 20/24 (83) |

a Duration data missing for two patients.

*Reviewer's comments: While it is plausible that patients who necessitated the use of concomitant steroids may have had more severe disease, overall, the number of subjects who had concomitant steroids or had no history of smoking were too small to*

*allow any reliable conclusion on comparisons with respect to steroid use and smoking history.*

***Clinical Cure Rates by Pathogen***

In patients with microbiologically documented infection, the Satisfactory clinical response rate was 92% (95/103). Satisfactory clinical responses were obtained in 90% (61/68) of the Clinically Evaluable Patients with a single pre-treatment pathogen and in 97% (34/35) of the patients with multiple pre-treatment pathogens.

Satisfactory clinical responses were obtained in nearly all of the Clinically Evaluable Patients from whom one of the major respiratory pathogens was isolated pre-treatment: 97% (31/32) in patients with *H. influenzae*, 100% (11/11) in patients with *S. pneumoniae*, and 100% (12/12) in patients with *M. catarrhalis* (Table 6). In addition, very high Satisfactory clinical response rates were obtained in patients infected with other respiratory pathogens, specifically *H. parainfluenzae* (90%) and *S. aureus* (92%). Gatifloxacin was also clinically effective in patients from whom *K. pneumoniae*, *P. aeruginosa*, *E. cloacae*, *E. coli*, and a variety of other Gram-negative organisms were isolated. Two clinically evaluable patients from whom a gatifloxacin-resistant *P. aeruginosa* was isolated pre-treatment had clinical responses of Cured.



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Table 6 Satisfactory Clinical Response Rate by Pathogen, Pathogens from Clinically Evaluable Patients

| Pathogen[a]/Subtype | Number Satisfactory/Number Isolated (%) |
|---|---|
| *H. influenzae* | 31/32 (97) |
| β-Lactamase - | 22/23 (96) |
| β-Lactamase + | 7/7 (100) |
| β-Lactamase Unknown | 2/2 (100) |
| *M. catarrhalis* | 12/12 (100) |
| β-Lactamase - | 2/2 (100) |
| β-Lactamase + | 10/10 (100) |
| *H. parainfluenzae* | 9/10 (90) |
| β-Lactamase - | 5/5 (100) |
| β-Lactamase + | 1/1 (100) |
| β-Lactamase Unknown | 3/4 (75) |
| *S. pneumoniae* | 11/11 (100) |
| Penicillin Sensitive | 8/8 (100) |
| Penicillin Intermediate | 1/1 (100) |
| Penicillin Resistant | 1/1 (100) |
| Penicillin Susceptibility Unknown | 1/1 (100) |
| *S. aureus* | 11/12[b] (92) |
| *K. pneumoniae* | 7/9 (78) |
| *P. aeruginosa* | 8/8 (100) |
| *E. cloacae* | 6/6 (100) |
| *E. coli* | 5/5 (100) |
| Other Gram-Negative | 32/35[c] (91) |
| Other Gram-Positive | 1/1 (100) |
| TOTAL | 133/141 (94) |

[a] A patient may have had more than one pathogen isolated pre-treatment.

[b] Reflects only the Clinically Evaluable Patients whose pre-treatment Gram stain suggested that *S. aureus* was the causative pathogen. Clinical response was Satisfactory in five of the other six Clinically Evaluable Patients who had *S. aureus* isolated pre-treatment in which the Gram stain suggested colonization.

[c] Consisted of 17 organisms.

***Reviewer's comments:*** *Reviewer agrees with the data presented in this table via the databases. The majority of the organisms were presumed eradicated. Data show that satisfactory clinical responses were achieved for the 5 most frequently isolated organisms, specifically H. influenzae, S. pneumoniae, M. catarrhalis, H. parainfluenzae and S. aureus.*

***Relapses, Clinically Evaluable Patients***

Two Clinically Evaluable Patients had clinically documented relapses of their acute exacerbation. Sputum cultures were not done. Both patients were given an alternative antibiotic plus a steroid.

***New Infections***

Twenty (12%) Clinically Evaluable Patients developed new infections. Among these patients, there were a total of 22 new infections (twelve of the genitourinary system, eight of the respiratory system, and two of the gastrointestinal system). Two patients developed two new infections each: one developed both oral and vaginal candidiasis, and the other developed both pharyngitis and a urinary tract infection.

Five (3%) patients experienced new episodes of AECB. The other new infections of the respiratory tract were one case each of pharyngitis, pneumonia and sinusitis. New infections of the gastrointestinal tract consisted of two cases of oral candidiasis.

Nine patients developed vaginal infections; one of these patients was diabetic. Three of the nine patients developed vaginal infections during gatifloxacin treatment. Eight of the nine patients were treated with antifungals, primarily topical, with resolution of symptoms. The ninth patient had resolution of her vaginal infection without therapy. Three patients developed UTI.

## Micobiologically Evaluable Patients

***Bacteriologic Response***

Overall, gatifloxacin achieved eradication of 96% (134/139) of the pre-treatment pathogens isolated from Microbiologically Evaluable Patients (Table 7). In the great majority of cases, pathogen eradication was presumed (i.e., based on the clinical response). All isolates of *H. influenzae* (32), *S. pneumoniae* (11) and *M. catarrhalis* (12) from Microbiologically Evaluable Patients were eradicated. In addition, all (12/12) of the *S. aureus* isolates and 90% (9/10) of *H. parainfluenzae* isolates were eradicated. Gatifloxacin was also effective in eradicating *K. pneumoniae*, *P. aeruginosa*, *E. cloacae*, *E. coli*, and a variety of other Gram-negative organisms.

Four pre-treatment pathogens were presumed persistent, i.e., the bacteriologic response for each was Presumed Persisted based on an Unsatisfactory clinical response for the corresponding patient. The four presumed persistent pathogens were: one strain each of *H. parainfluenzae* (β-lactamase status unknown) and *K. pneumoniae*, and two strains of *Haemophilus* species. In addition, one of the pre-treatment *S. aureus* strains not considered a causative pathogen was presumed persistent (bacteriologic response of Presumed Persisted).

Table 7 Bacteriologic Eradication Rate by Pathogen, Pathogens from Microbiologically Evaluable Patients

| Pathogen[a]/ Subtype | Number Isolated | Number (%) Eradicated | | |
|---|---|---|---|---|
| | | Total | Documented | Presumed |
| *H. influenzae* | 32 | 32 (100) | 3 (9) | 29 (91) |
| β-Lactamase - | 23 | 23 (100) | 3 (13) | 20 (87) |
| β-Lactamase + | 7 | 7 (100) | 0 | 7 (100) |
| β-Lactamase Unknown | 2 | 2 (100) | 0 | 2 (100) |
| *M. catarrhalis* | 12 | 12 (100) | 0 | 12 (100) |
| β-Lactamase - | 2 | 2 (100) | 0 | 2 (100) |
| β-Lactamase + | 10 | 10 (100) | 0 | 10 (100) |
| *H. parainfluenzae* | 10 | 9 (90) | 1 (10) | 8 (80) |
| β-Lactamase - | 5 | 5 (100) | 0 | 5 (100) |
| β-Lactamase + | 1 | 1 (100) | 0 | 1 (100) |
| β-Lactamase Unknown | 4 | 3 (75) | 1 (25) | 2 (50) |
| *S. pneumoniae* | 11 | 11 (100) | 0 | 11 (100) |
| Penicillin Sensitive | 8 | 8 (100) | 0 | 8 (100) |
| Penicillin Intermediate | 1 | 1 (100) | 0 | 1 (100) |
| Penicillin Resistant | 1 | 1 (100) | 0 | 1 (100) |
| Penicillin Susceptibility Unknown | 1 | 1 (100) | 0 | 1 (100) |
| *S. aureus* | 12[b] | 12 (100) | 1 (8) | 11 (92) |
| *K. pneumoniae* | 9 | 8 (89) | 1 (11) | 7 (78) |
| *P. aeruginosa*[c] | 6 | 5 (83) | 0 | 5 (83) |
| *E. cloacae* | 6 | 6 (100) | 0 | 6 (100) |
| *E. coli* | 5 | 5 (100) | 0 | 5 (100) |
| Other Gram-Negative | 35[d] | 33 (94) | 2 (6) | 31 (89) |
| Other Gram-Positive | 1 | 1 (100) | 0 | 1 (100) |
| TOTAL | 139 | 134 (96) | 8 (6) | 126 (91) |

[a] A patient may have had more than one pathogen isolated pre-treatment.

[b] Reflects only those pre-treatment isolates from Microbiologically Evaluable Patients in which the Gram stain suggested that *S. aureus* was the causative pathogen. Bacteriologic response was Presumed Eradicated for five of the other six pre-treatment *S. aureus* isolates from Microbiologically Evaluable Patients in which the Gram stain suggested colonization; the other bacteriologic response was Presumed Persisted.

[c] One isolate had a microbiologically documented response of Persisted.

[d] Consisted of 17 organisms.

***Reviewer's comments:*** *Reviewer agrees with the data above via the databases. The applicant's data demonstrate efficacy over the 5 most frequently isolated pathogens, namely H. influenzae, S. pneumoniae, M. catarrhalis, H. parainfluenzae and S. aureus; however, the fact that in most cases eradication was presumed and not microbiologically*

*documented weakens the strength of evidence. Since the role of S. aureus in AECB is not entirely clear, a closer look at patients with this organism showed that only 7 patients had a pure growth of S. aureus, 5 of which had a presumed bacteriological eradication and one a confirmed eradication.*

## Eligible Patients

*Clinical Efficacy*

Eighty percent of the Eligible Patients had a Satisfactory clinical response (Table 8). Sixty-five percent of the patients were assessed as Cured and 16% of the patients were considered Improved. Sixteen (9%) patients had a response of Unable to Determine.

Table 8 Clinical Response, Eligible Patients

| | Number (%) of Patients | |
|---|---|---|
| Clinical Response | N = 178 | 95% Confidence Interval |
| Satisfactory | 143 (80) | (74 %, 86%) |
| Cured | 115 (65) | (57%, 72%) |
| Improved | 28 (16) | |
| Unsatisfactory | 19 (11) | |
| Unable to Determine | 16 (9) | |

***Reviewer's comments:*** *For 5 patients at a single site, the investigator's assessment was Cured but the patients' symptoms were mistakenly entered as Improved by the investigator. The investigator later changed the symptoms response to Resolved, but this was done after the applicant's medical monitor had entered the response as Improved into the database. This discrepancy was displayed by the applicant in an appendix. If those patients were to be entered as Cured, the cure rate would rise to 68% (120 out of 178) and the improvement rate would decrease to 13% (23 out of 178). The adjusted CI would be 60% - 74%, which is considered acceptable by the reviewer for the indication of AECB.*

*Bacteriologic Efficacy*

Overall, gatifloxacin achieved eradication of 88% (135/154) of the pre-treatment pathogens isolated from Eligible Patients. In the great majority of cases, pathogen eradication was presumed (i.e., based on the clinical response). All of the *S. pneumoniae* (11) and *M. catarrhalis* (12) isolates, and 89% (32/36) of the *H. influenzae* isolates were eradicated. In addition, 75% (9/12) of the *H. parainfluenzae* isolates and 87% (13/15) of the *S. aureus* isolates were eradicated.

***Reviewer's comments:*** *Reviewer agrees with these data via the databases. The applicant's data demonstrate efficacy over the 5 most frequently isolated pathogens, namely H. influenzae, S. pneumoniae, M. catarrhalis, H. parainfluenzae and S. aureus.*

**8.2.1.4.3 Safety Evaluation**

*All Adverse Clinical Events (ACE)*

Ninety-two (44%) patients experienced one or more adverse clinical events (Table 9). In 52 (25%) patients the adverse clinical events were not related to gatifloxacin, while in 40 (19%) patients at least one ACE was considered to be drug-related by the Investigators (no ACE was considered of unknown relationship to gatifloxacin). The most common adverse clinical events were headache (10% of patients), vaginitis (9% of females), dyspnea (8% of patients), nausea (7%), increased sputum (6%) and increased coughing (6%).

Ten female patients developed vaginitis; they ranged in age from 24 to 74 years old (median: 42.5 years). One of these patients was diabetic. Four episodes were described as mild, five as moderate, and one as severe. Nine of the vaginitis patients were treated with topical antifungal creams; one also received fluconazole. All of their infections resolved. The tenth vaginitis patient had resolution of symptoms without treatment.

*Drug-Related Adverse Clinical Events*

The incidence of adverse clinical events assessed by the Investigator to be related to gatifloxacin was 19% (40 patients) (Table 10). The most common were vaginitis (8% of females), nausea (4% of patients), dizziness (2%), dry mouth (2%) and headache (2%). Most gatifloxacin-related adverse clinical events were mild (23 patients, 11%) or moderate (14 patients, 7%) in severity. Three (1%) patients experienced a total of four severe ACE. There was one event each of severe vaginal candidiasis, sinus congestion severe diaphragmatic cramping and diaphoresis. Gatifloxacin therapy was not discontinued in these three patients.

*Deaths and Serious Adverse Events (SAE)*

One patient died of a myocardial infarction 24 days after completing gatifloxacin therapy. He was 72 years old and had a history of coronary artery disease, COPD, and anxiety. The patient's death was judged not related to gatifloxacin by the Investigator.

Five (2%) patients experienced 11 serious adverse events on study, none of which were related to gatifloxacin according to the Investigators. There were one case each of congestive heart failure, atrial fibrillation, myocardial infarction, syncope, nausea, abdominal pain, vomiting, bronchitis, COPD exacerbation, dyspnea and accidental injury. The latter involved elective surgery (after the TOC Visit) for a chronic knee ailment. Two of the five patients discontinued gatifloxacin therapy as a result of their serious adverse events.

Table 9 Adverse Clinical Events of All Causes, by Investigator's Assessment of Relationship to Gatifloxacin, All Treated Patients

| | Number (%) of Patients (N = 210) | | |
|---|---|---|---|
| Adverse Clinical Event[a] | Drug-related | Not Drug-related | Total |
| Any Adverse Clinical Event | 40 (19) | 52 (25) | 92 (44) |
| Headache | 4 (2) | 16 (8) | 20 (10) |
| Dyspnea | 0 | 16 (8) | 16 (8) |
| Nausea | 9 (4) | 5 (2) | 14 (7) |
| Increased Sputum | 0 | 13 (6) | 13 (6) |
| Increased Coughing | 0 | 13 (6) | 13 (6) |
| Chest Pain | 0 | 11 (5) | 11 (5) |
| Vaginitis | 9 (8)[b] | 1 (<1)[b] | 10[c] (9)[b] |
| Rhinitis | 1 (<1) | 9 (4) | 10 (5) |
| Pharyngitis | 0 | 9 (4) | 9 (4) |
| Respiratory Disorder | 0 | 9 (4) | 9 (4) |
| Dizziness | 5 (2) | 3 (1) | 8 (4) |
| Vomiting | 2 (1) | 4 (2) | 6 (3) |
| Diarrhea | 2 (1) | 3 (1) | 5 (2) |
| Malaise | 0 | 5 (2) | 5 (2) |
| Dry mouth | 5 (2) | 0 | 5 (2) |
| Chills | 0 | 4 (2) | 4 (2) |
| Dyspepsia | 1 (<1) | 3 (1) | 4 (2) |
| Rales[d] | 0 | 4 (2) | 4 (2) |

[a] All adverse clinical events occurring in 2% of the total number of treated patients.
[b] Percent based on 106 female patients.
[c] Eight of the 10 patients who developed vaginal infections were reported to have "vaginitis" and two were reported to simply have "infection". The adverse events in these two categories have been combined and reported here under the term "vaginitis".
[d] Four patients with rales plus one patient with COPD exacerbation had been assigned the COSTART term "lung disorder". For clarity, the separate non-COSTART terms were used. COPD exacerbation was below the 2% threshold, so that adverse clinical event is not reflected in the table.

Table 10 Drug-related Adverse Clinical Events According to the Investigators, All Treated Patients

| | Number (%) of Patients | | | |
|---|---|---|---|---|
| Drug-related Adverse Clinical Event[a] | Mild | Moderate | Severe | Total |
| Any Drug-related Adverse Clinical Event | 23 (11) | 14 (7) | 3 (1) | 40 (19) |
| Vaginitis | 3 (3)[b] | 5 (5)[b] | 1 (<1)[b] | 9 (8)[b] |
| Nausea | 6 (3) | 3 (1) | 0 | 9 (4) |
| Dizziness | 3 (1) | 2 (1) | 0 | 5 (2) |
| Dry mouth | 5 (2) | 0 | 0 | 5 (2) |
| Headache | 4 (2) | 0 | 0 | 4 (2) |
| Diarrhea | 2 (1) | 0 | 0 | 2 (1) |
| Moniliasis Oral | 1 (<1) | 1 (<1) | 0 | 2 (1) |
| Pain | 0 | 1 (<1) | 1 (<1) | 2 (1) |
| Vomiting | 1 (<1) | 1 (<1) | 0 | 2 (1) |
| Depersonalization | 1 (<1) | 0 | 0 | 1 (<1) |
| Depression | 1 (<1) | 0 | 0 | 1 (<1) |
| Diaphoresis | 0 | 0 | 1 (<1) | 1 (<1) |
| Dyspepsia | 0 | 1 (<1) | 0 | 1 (<1) |
| Flatulence | 0 | 1 (<1) | 0 | 1 (<1) |
| Glossitis | 1 (<1) | 0 | 0 | 1 (<1) |
| Nervousness | 1 (<1) | 0 | 0 | 1 (<1) |
| Palpitation | 1 (<1) | 0 | 0 | 1 (<1) |
| Ptosis | 1 (<1) | 0 | 0 | 1 (<1) |
| Rhinitis | 0 | 0 | 1 (<1) | 1 (<1) |
| Somnolence | 0 | 1 (<1) | 0 | 1 (<1) |
| Stomatitis | 0 | 1 (<1) | 0 | 1 (<1) |
| Taste Perversion | 1 (<1) | 0 | 0 | 1 (<1) |
| Vasodilation | 1 (<1) | 0 | 0 | 1 (<1) |

[a] All drug-related adverse clinical events experienced by All Treated Patients are included.
[b] Percent based on 106 female patients.

### *Adverse Events Leading to Discontinuation of Study Therapy*

Of the 210 patients who received at least one dose of gatifloxacin, seven (3%) discontinued treatment due to adverse clinical events and one due to a laboratory test abnormality at baseline. Four of the adverse events were considered by the Investigators to be gatifloxacin related: one instance each of vaginitis, nausea, dyspepsia and

abdominal pain. One patient was discontinued after having received three doses of gatifloxacin when the Investigator noted at the during-study visit that the patient's pre-treatment creatinine value was elevated (1.8 mg/dL). No follow-up renal function studies were obtained for this patient.

***Reviewer's comments:*** *Most adverse events were non-serious in nature. Class-related events, namely phototoxicity, tendinitis, and seizures, were not encountered. Discontinuations were infrequent. The one death occurrence seemed unrelated to gatifloxacin but such a relation cannot be definitely excluded. From this study, it appears that gatifloxacin has a favorable adverse clinical event profile.*

***Laboratory Test Results***

Patients with Normal Pre-treatment Values

Very few patients with normal baseline values developed abnormal laboratory test results during or post-treatment. The abnormalities that did occur usually were mild. The most common abnormalities were increased bicarbonate (9% of 114 tested), ALT (7% of 184 tested), AST (5% of 178 tested) , and glucose (6% of 17 tested) and decreased bicarbonate (9% of 114 tested).

Hyperglycemia was noted in one of the 17 patients (6%) who had fasting glucose levels measured before treatment and during and/or after treatment. That patient had a pre-treatment fasting glucose level of 81 mg/dL that rose to 127 mg/dL on Day 5 of gatifloxacin therapy. At the post-treatment visit (Day +10) the value had decreased to 93 mg/dL. No history of diabetes mellitus was elicited.

Seven patients of 165 tested (4%) developed Grade 1 amylase levels either during (one patient) or post-treatment (six patients). Three of these patients regularly used alcohol. None of the seven patients reported abdominal pain at the time of the amylase elevations, nor were any diagnosed with pancreatitis.

Seven patients of 196 tested (3%) had at least one Grade 1 creatinine elevation during or post-treatment. Only one developed a level greater than 1.8 mg/dL. This occurred in a 72 year-old patient who had pre-treatment creatinine value of 1.4 mg/dL. In addition, 6-10 WBC per LPF and 6-10 RBC per LPF were detected on microscopic urinalysis at that time. The patient's creatinine value rose to 1.9 mg/dL during treatment (Day 5), and to 2.2 mg/dL post-treatment (Day +9). No urinalysis was obtained at these visits. The patient subsequently expired of an acute myocardial infarction.

Development of a Grade 3 or Grade 4 laboratory test elevation occurred in only two patients: each developed Grade 3 hypochloremia (Day 4 and Day +9, respectively). Both patients were taking diuretics.

Patients with Abnormal Pre-treatment Values

Patients who had abnormal (Grade 1, 2 or 3) pre-treatment laboratory values occasionally experienced worsening to a higher grade during or post-treatment. However, worsening to a Grade 3 or Grade 4 result was rare. This occurred in only one patient for two different tests: an HIV-positive man on zidovudine, entered the study with Grade 2 leukopenia and Grade 2 neutropenia, which worsened to Grade 3 and Grade 4, respectively, on Day +10 (no follow-up available).

Four patients entered the study with abnormal creatinine levels (three Grade 1, one Grade 2), but none experienced a worsening in creatinine level during or after gatifloxacin treatment.

***Reviewer's comments:*** *Gatifloxacin appears to have a favorable adverse event profile in terms of laboratory parameters. Hepatic and renal abnormalities were infrequent and mild. Among patients with normal pre-treatment values, 9 of 178 tested for both AST and ALT (5%) had an elevation of both, and 2 of them also had an elevated Alkaline Phosphatase. None had a concomitant elevation of bilirubin. Only 17 patients had a pre and post-treatment Fasting Blood Sugar done. Twenty two patients receiving theophylline had their serum theophylline levels monitored. No value was found to be outside the therapeutic range. Worsening of neutropenia in a patient on zidovudine is unlikely to be due to an interaction between gatifloxacin and zidovudine based on the current knowledge about these 2 drugs.*

## 8.2.1.5 Conclusions

The applicant's conclusion was that "the results of this study indicate that gatifloxacin 400 mg daily for 10 days is safe and effective for the treatment of acute exacerbations of chronic bronchitis. The drug demonstrated a favorable safety profile and excellent clinical and bacteriologic efficacy in a highly representative cohort of patients with this disease. Efficacy was documented for the respiratory pathogens *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*, as well as for *H. parainfluenzae* and *S. aureus*".

***Reviewer's comments:*** *Data in this study were well presented in tables and appendices in hard copy and electronic format, which allowed easy derivation for further analysis. Individual patient data were well documented on Case Report Forms, as shown by a thorough review of 10% of those. Data regarding clinical and microbiologic efficacy were supportive of effectiveness against the major pathogens involved in AECB, namely H. influenzae, S. pneumoniae and M. catarrhalis, but also against S. aureus and H. parainfluenzae. The safety profile seemed favorable but should be examined more thoroughly through the review of the data from the other 2 controlled studies in AECB as well as the integrated safety summary.*

## 8.2.2 Trial #2

Applicant's Study AI420-001: A Randomized, Double-Blind, Multicenter Comparative Study of Gatifloxacin Versus Levofloxacin in the Treatment of Acute Exacerbations of Chronic Bronchitis (AECB).

### 8.2.2.1 Rationale/Objective

An open-label Phase II study with gatifloxacin 400 mg PO QD in the treatment of AECB (AI420-004) was already conducted in the United States. There was a good response rate and the majority of adverse events were considered mild.

The objectives of this study (AI420-001) were to demonstrate clinical efficacy and safety of gatifloxacin in AECB relative to a standard regimen of levofloxacin, and to demonstrate microbiological eradication rates and responses for the most common pathogens causing AECB.

### 8.2.2.2 Design

This was a randomized, double-blind, multicenter study designed to assess the safety and efficacy of gatifloxacin at a dose of 400 mg PO QD for 7-10 days versus a standard regimen of levofloxacin, 500 mg PO QD for 7-10 days in the treatment of adult patients with AECB. Twenty-six study sites in the US were recruited, 20 enrolled patients. Patients were stratified at the time of randomization based on their smoking status. A patient was considered a current smoker if he or she was a smoker at the time of enrollment or had stopped smoking within the two months before enrollment. The target enrollment was 356 patients.

Sample size was initially determined using a cure rate of 64% for levofloxacin in an evaluable patient population with AECB. Assuming equivalence in response rates between the two treatment groups and 90% power to rule out a maximum difference of 20%, 120 evaluable patients per arm were needed (150 patients per arm assuming an 80% evaluability rate for a total of 300 patients).

To evaluate whether or not sample size needed to be increased due to differences in clinical response or evaluability rate from the original assumptions, the sample size was reassessed when investigator clinical responses from 160 patients were available in the study database. Based on the pooled (blinded) response rate of 93% and the observed evaluability rate of 77%, the revised calculations indicated 137 evaluable patients per arm were needed. Based on this calculation the target sample size was increased to a total accrual of 356 patients.

The randomization system used the Pocock minimization algorithm, which adjusted the randomization probabilities in order to minimize any imbalance of treatment arms within each site, within each smoking group and for the overall study.

***Reviewer's comments:*** *This trial attempts to establish equivalence of gatifloxacin to an approved drug for the indication of AECB. The study design uses an active control drug and a random assignment of patients to the investigational drug and the active control drug groups in a double-blind fashion. This is the preferred design according to the IDSA/FDA "Guidelines For The Evaluation Of Anti-Infective Drug Products".*

## 8.2.2.3 Protocol

### 8.2.2.3.1 Population

For inclusion, patients with a history of chronic bronchitis (i.e., productive cough on most days for at least three consecutive months in two consecutive years) and a diagnosis of AECB had to meet all of the following criteria:

- Eighteen years of age or older;
- Clinical diagnosis of acute exacerbation of chronic bronchitis, defined as:
  - The presence of purulent sputum confirmed by Gram stain examination [>25 polymorphonuclear leukocytes (PMN) and <10 squamous epithelial cells (epi) per low power field (LPF)]
  - The presence of at least two of the following signs and symptoms:
    - increased cough and/or dyspnea;
    - increased sputum volume;
    - increased sputum purulence.
- For women of childbearing potential:
  - A negative urine pregnancy test within two days prior to enrollment,
  - Commitment to use an effective method of contraception from the start of study treatment until the end of their participation in the study;
- Written informed consent (from patients or their guardians) before any study procedures were performed.

Patients were excluded if they met any of the following criteria:

- Pregnant or lactating
- History of significant hypersensitivity reaction to either fluoroquinolone compounds
- Received a systemic antibiotic therapy within seven days prior to enrollment, or were likely to require other systemic antibiotic(s) concomitantly
- Diagnosis of pneumonia confirmed by the presence of pulmonary infiltrates on a chest x-ray

- Previously diagnosed disease(s) of immune function (e.g., AIDS or history of clinical manifestations of HIV infection, neutrophil count < 1000/mm$^3$)
- Previously diagnosed condition that would tend to mimic or complicate the course and evaluation of the infectious process
- Known renal insufficiency (i.e., serum creatinine ≥1.5 mg/dL or requiring renal dialysis);
- Current clinically significant hepatic disease (i.e., aspartate amino transferase (AST) and/or alanine amino transferase (ALT) and/or total bilirubin ≥3 times the upper limit of normal);
- Malabsorption syndromes or other gastrointestinal disturbances that would affect drug absorption;
- Previous treatment in any gatifloxacin study.

***Reviewer's comments:*** *Inclusion and exclusion criteria were appropriate and clearly identified prior to initiation of the study. The criterion of <10 epithelial cells/LPF was later relaxed by the applicant via the analysis plan to include patients who were shown at the central laboratory reading of the sputum Gram stain to have >10 epithelial cells/LPF. The applicant's explanation was that "epithelial cells, when associated with >25 PMNs, only indicate that the purulent bronchial secretions have been contaminated by mouth flora. It does not detract from the clinical findings and confirms that the patient has purulent sputum". The applicant also cited a precedent where disregard of this criterion was acceptable to FDA, and provided FDA with a list of those patients who were enrolled despite having >10 epithelial cells/LPF. The exclusion of patients with AIDS, renal insufficiency and hepatic disease makes it difficult to predict safety and efficacy in these population groups.*

Exacerbation type at entry was determined according to the following criteria established by Anthonisen, et al.

- Type I - increased dyspnea, increased sputum volume and increased sputum purulence;
- Type II - any two of the three symptoms of Type I;
- Type III - any one of the three symptoms of Type I.

Patients received gatifloxacin 400 mg PO once a day or levofloxacin 500 mg PO once a day with placebo. The duration of therapy, i.e. 7-10 days, was to be decided by the investigator at the Day 3 to 5 visit.

Patients were to be excluded if they had received antibiotic therapy within 7 days before enrollment. Other antimicrobial agents, such as antivirals and antifungals, were permitted pre-treatment. Adjunctive measures, such as oral or topical decongestants, antihistamines, and intranasal steroids, were permitted during and post-treatment as needed by the patient. In addition, concomitant or post-treatment non-drug therapies,

such as postural drainage or oxygen were allowed. Investigators were permitted to discontinue study drug and remove patients from the study for the following reasons:

- An adverse event;
- Persistence or worsening of signs and symptoms of the acute infection after 3 days of study drug therapy;
- An intercurrent illness;
- Patient's decision not to participate any further;
- Investigator's decision that discontinuation was in the patient's best interest;
- A female patient with a positive pregnancy test during study drug therapy (immediate discontinuation);
- Decision of the sponsor to terminate the study (at some or all sites).

Patients with one or more study drug-resistant pre-treatment pathogens were removed from the study if the investigator felt it was in their best interest. Patients whose condition had not improved or had worsened after 3 days of study drug therapy (early treatment failures) were removed from the study. These patients had the same clinical and laboratory procedures performed as those specified for the post-treatment visit scheduled for Day +7 to Day +14 before starting alternative antibiotic therapy.

Clinical and bacteriologic responses to gatifloxacin therapy were assessed at Day +7 to Day +14 post-treatment visit, or earlier for those who discontinued therapy prematurely. Clinical response to gatifloxacin therapy was based upon the signs and symptoms of the acute infection; the bacteriologic response for each pre-treatment pathogen was based on culture results or, if there was no source to culture, the clinical assessment at the Test of Cure (TOC) visit. Relapse was evaluated at the Day +21 to Day +28 extended follow-up assessment.

Patient assessments were scheduled to occur as follows (Table 1):

- Pre-treatment (within 48 hours before dosing) office/clinic visit;
- During treatment (Day 3 to Day 5) office/clinic visit;
- End of treatment (Day +1 to Day +3) office/clinic visit;
- Post-treatment (Day +7 to Day +14) telephone contact (office/clinic visit for further evaluation if not clinically improved); and
- Extended Follow-up (Day +21 to Day +28) office/clinic visit.

Table 1 Flow Chart: Schedule of Patient Assessments

| Procedure | Pre-treatment (Within 2 days prior to dosing) | During Treatment (Days 3 to 5) | End of Treatment a (Days +1 to +3) | Post-treatment (Days + 7 to +14) | Extended Follow-up[a] (Days + 21 to +28) |
|---|---|---|---|---|---|
| Screening | X | - | - | - | - |
| Chest X-Ray | X | X[b] | - | X[b] | - |
| Medical History | X | - | - | - | - |
| Physical Exam | X | - | - | X | - |
| Vital Signs | X | X | - | X | - |
| Clinical Evaluation | X | X | X | X | X[c] |
| Laboratory Tests | X | X | - | X | - |
| Sputum Smear and Evaluation | X | X | - | X | X[c] |
| Sputum Culture | X | X | - | X | X[c] |
| Assess Adverse Events | - | X | X | X | X |
| Assess Medication Use | - | X | X | X | - |
| Pregnancy Test | X | - | - | X | - |

[a] Telephone contact. If patient not clinically improved, office visit to be scheduled for further evaluation.

[b] If clinically indicated.

[c] Office visit to be scheduled for further evaluation if increased sputum production persisted. Culture to be done if purulent sputum specimen obtained.

All laboratory procedures, including appropriate cultures, were performed by a central laboratory. Investigators performed initial Gram stain procedures on site to expedite determination of sputum purulence and, therefore, patient eligibility. The central laboratory performed an independent Gram stain. If the site reading did not match the central laboratory, the Medical Monitor used the overread done by the central laboratory for determining patient eligibility.

All sputum specimens were plated semi-quantitatively for aerobic growth, and all potential pathogens isolated were tested for susceptibility to gatifloxacin and levofloxacin. Hematology, serum chemistry, and urinalysis tests included: White blood cell count (WBC) with differential, hemoglobin, hematocrit, platelet count, AST, ALT, total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, glucose, amylase, sodium, potassium, chloride, bicarbonate, qualitative urinalysis, microscopic urinalysis. A urine pregnancy test was performed on all women of childbearing potential. Positive urine pregnancy tests were confirmed with a serum-based pregnancy test.

All pre-treatment procedures were performed within two days prior to the start of study medication. Patients were observed at least once during treatment (between Day 3 and Day 5, inclusive), and as frequently as deemed necessary by the investigator. If a sputum specimen was produced during this visit, purulence was assessed and, if purulent, the specimen was plated semi-quantitatively for aerobic growth and antibiotic susceptibility. A chest x-ray was taken if clinically indicated.

In the three-day period immediately following the end of therapy (i.e., Day +1 to Day +3, inclusive), patients were contacted by telephone and queried about the clinical signs and symptoms of infection, the occurrence of adverse events, and compliance with the dosing regimen. If a patient's signs and symptoms had not returned to baseline, or if clear clinical improvement had not occurred, the patient was scheduled for an immediate office visit. Clinical and laboratory procedures planned for the post-treatment patient visit scheduled for Day +7 to Day +14 were performed at that time.

Between seven and fourteen days post-treatment (i.e., Day +7 to Day +14, inclusive), patients were evaluated in the office/clinic for clinical and bacteriologic response to study drug therapy and the occurrence of adverse clinical events. If a patient was still producing sputum, a specimen was obtained for assessment of purulence, quantitative culture and susceptibility testing. If a laboratory test result became abnormal or worsened from an abnormal pre-treatment level, the test was repeated at appropriate intervals until the value either returned to the pre-treatment level or stabilized.

Patients who had a clinical response of cured at the Day +7 to Day +14 post-treatment visit were contacted by telephone approximately two weeks later (i.e., Day +21 to Day +28, inclusive) to assess relapse of the acute infection. Patients were queried about the presence and severity of clinical signs and symptoms of infection, the ingestion of any antibiotics since the last office/clinic visit, and the occurrence of adverse clinical events. If increased sputum production persisted, or recurred after initial improvement, an office/clinic visit was scheduled for further evaluation. This included collection of a sputum sample for assessment of appearance and evaluation of a Gram-stained smear; if the specimen was purulent, bacteriologic culture and susceptibility testing of any isolated pathogens were performed.

*Reviewer's comments: Patient monitoring was adequate in terms of frequency of visits and phone check-ups. Laboratory tests were also adequate for proper detection of toxicity. Study drug levels were not measured to verify compliance, which was only done through a patient maintained diary. Reliance on a central laboratory minimizes inter-site variability and ensures consistency of test results.*

## 8.2.2.3.2 Endpoints

Clinical and bacteriologic responses were determined from data at the TOC visit scheduled between Day +7 and Day +14, inclusive. In the analysis, due to potential schedule conflicts, any visit from Day +5 to Day +18, inclusive, was acceptable.

Treatment failures could be assessed at any time prior to Day +18, but patients had to receive a minimum of 3 days of therapy.

***Reviewer's comments:*** *The TOC window of +7 to +14 days was expanded to +5 to +18 days. This was done to allow for any difficulties in the patient scheduling an office visit. This change was made with the understanding that the lower value of the TOC window would still be greater than 5 half-lives of gatifloxacin, and it was done prior to datalock and unblinding of the study. This expansion did not affect the interpretation of the study results.*

Investigators assigned a clinical response to each patient and a bacteriologic response to each pre-treatment pathogen.

*Clinical Response*

Each patient was assigned a clinical response of Cured, Failure, or Unable to Determine (UTD).

CURED:

- All signs and symptoms related to the acute infection (cough, dyspnea, sputum production, and sputum purulence) have improved or returned to the patient's baseline level with the original therapy alone without need for further antimicrobials; and
- No new signs or symptoms of acute infection were present.

(Note: Baseline is defined as the patient's assessment of their typical/usual condition when free of acute infection)

FAILURE:

- Signs and symptoms related to the acute infection (cough, dyspnea, sputum production, or sputum purulence) did not improve after 3 days of study therapy; or
- New clinical signs and symptoms of acute infection were present; or
- If present at study entry, fever persisted (i.e., temperature >38.0°C); or
- The patient was removed from the study and placed on alternate antibiotic therapy because of persistent, worsened or new signs and symptoms of acute infection after at least 3 days of study therapy; or
- Clinical/radiological evidence of pneumonia; or
- Another antibiotic is required for treatment of this acute episode despite the resolution of signs and symptoms.

UNABLE TO DETERMINE:

- No post-treatment evaluation of signs and symptoms was done (i.e., no TOC visit); or

- The patient received another systemic antibiotic with documented (i.e., in the package insert) activity against the pre-treatment pathogen, for an infection other than bronchitis, prior to the TOC visit.

***Bacteriologic Response***

Each pre-treatment pathogen was assigned a bacteriologic response of Eradicated, Presumed Eradicated, Persisted, Presumed Persisted or Unable to Determine:

ERADICATED:

- The original pathogen was absent from the culture of a good quality sputum specimen (i.e., >25 PMN per LPF) obtained at the TOC visit.

PRESUMED ERADICATED:

- No post-treatment culture was performed and the clinical response was cured;
- The patient was not producing sputum (i.e., there was no source to culture) at the TOC visit and the clinical response was Cured.

PERSISTED:

- The original pathogen was present in the culture of a good quality sputum specimen (i.e., >25 PMN per LPF) obtained at the TOC visit.

PRESUMED PERSISTED:

- No post-treatment culture was performed and the clinical response was failure;
- The patient was not producing sputum (i.e., there was no source to culture) at the TOC visit and the clinical response was Failure.

UNABLE TO DETERMINE:

- No post-treatment evaluation was done (i.e., no TOC visit); or
- The patient received another systemic antibiotic with documented (i.e., in the package insert) activity against the pre-treatment pathogen, for an infection other than bronchitis, prior to the TOC visit; or
- The patient did not receive a minimum of 3 days of therapy; or
- The patient's pre-treatment pathogen was resistant to either study treatment; or
- The clinical response of the patient in question was designated Unable to Determine.

*Relapse*

Patients who had a clinical response of Cured at the time of the TOC visit were evaluated for relapse at the extended follow-up assessment (Day +21 to Day +28). Relapse was defined as:

- Worsening, or recurrence after initial improvement/resolution, of the signs and symptoms related to the acute infection (cough, dyspnea, sputum production, sputum purulence); or
- Appearance of new clinical signs and symptoms of acute respiratory infection without documentation of a new pathogen; or
- Persistence, worsening or emergence of new signs and symptoms of acute bronchial infection requiring alternate antibiotic therapy.

Pathogens isolated from relapsed patients were speciated and tested for susceptibility to gatifloxacin, levofloxacin and other antibiotics as appropriate.

*New Infections*

A new infection was defined as the occurrence, at any time during or after gatifloxacin therapy, of one of the following:

- Isolation of any pathogen from a new site of infection, with associated clinical signs and symptoms;
- The presence of clinical signs and symptoms indicative of a new infection for which a culture would not usually be obtained (e.g., skin infection).

Pathogens isolated from patients with new infections were speciated and tested for susceptibility to gatifloxacin, levofloxacin and other antibiotics as appropriate.

Safety Variables and deaths were collected between the first day of study drug treatment and 30 days after the last day of study drug treatment, inclusive.

*Adverse Clinical Events*

Investigators reported all adverse clinical events to the Sponsor, along with their judgment of the causality. For the purpose of analysis, events that were certainly, probably or possibly drug-related were grouped and categorized as "drug-related". Investigators also assessed the severity (mild, moderate, severe, or very severe) of each adverse clinical event.

*Abnormal Laboratory Results*

Any worsening in laboratory parameters during or post-treatment was categorized according to a severity grading scale derived from the National Cancer Institute's Common Toxicity Criteria (CTC) or the Acquired Immune Deficiency Syndrome (AIDS) Clinical Trials Group (ACTG) classification of laboratory abnormalities. Four grades of abnormality were defined (Grades 1-4), and the range of laboratory values associated with each grade was established for each test. Laboratory tests for which results were abnormal were to be repeated at appropriate intervals until the abnormal values returned

to pre-treatment levels or were deemed by the investigator to be unrelated to the study medication.

***Reviewer's comments:*** *Clinical, microbiologic and laboratory endpoints were adequately and accurately defined prior to study initiation.*

## 8.2.2.3.3 Statistical Considerations

### *Data Set Descriptions*

There were four study populations of interest:

- All Treated Patients: All patients who received at least one dose of study medication.
- Eligible Patients: All Treated Patients with a diagnosis of AECB at entry, defined as:
  - Having evidence of purulence in an adequate pre-treatment sputum sample (>25 PMN per LPF – the original inclusion criterion required <10 epithelial cells as well, but this criterion was relaxed as previously stated).
  - Having two or more of the following signs/symptoms of AECB:
    - increased dyspnea/cough;
    - increased sputum production;
    - increased sputum purulence.
  - Having a pre-treatment radiograph that did not show pneumonia.
- Clinically Evaluable Patients: All Eligible Patients who:
  - Had a duration of dosing of at least five days (at least 3 days for treatment failures);
  - Had a post-treatment clinical assessment within the Day +5 to Day +18 window for the TOC visit (except for failures); and
  - Did not receive a systemic antibacterial agent between the time of the pre-treatment visit and the post-treatment assessment.
- Microbiologically Evaluable Patients: All Clinically Evaluable Patients who had at least one pathogen isolated pre-treatment non-resistant (susceptible and intermediate) pre-treatment to either study drug.

***Reviewer's comments:*** *The 4 datasets are adequate and, except for the Test of Cure window and the relaxation of the sputum criterion, correspond to prospective definitions the sponsor and FDA had agreed upon.*

### *Statistical Analyses*

Analyses of the pre-treatment characteristics and study medication usage for All Treated, Eligible and Clinically Evaluable Patients by treatment group, were performed.

Prognostic factors were also summarized.

*Primary Efficacy Analysis*

The primary efficacy assessment was based on the analysis of clinical response in the clinically evaluable subset. Equivalence of gatifloxacin to the control regimen was determined using the 95% confidence interval (CI) around the difference in clinical cure rates (gatifloxacin – levofloxacin). The confidence intervals were computed using the DerSimonian and Laird procedure in which smoking status was used as a stratification factor. Gatifloxacin was to be considered equivalent to levofloxacin if the lower confidence limit was greater than or equal to the limit specified in Table 2. Which limit applied depended on the largest observed cure rate of the two treatment arms:

Table 2

| Observed Cure Rate | Lower Limit |
|---|---|
| ≥90% | -10% |
| ≥80% to <90% | -15% |
| <80% | -20% |

***Reviewer's comments:*** *In line with the recent July 1998 Anti-infective Advisory Committee meeting, the limit of equivalence will be considered independent of the observed response. Since -15% was discussed and agreed upon by the FDA in reference to all recently submitted gatifloxacin protocols, -15% will be used in determining equivalence in this study.*

*Secondary Efficacy Analysis*

Analysis of clinical cure rates was presented by pathogen and by prognostic factors in the Clinically Evaluable Patient population. Bacteriologic eradication rates as well as cure rates by pathogen were determined for the microbiologically evaluated patients. Ninety-five percent confidence intervals (CIs) were constructed around the clinical Cure rates for Clinically Evaluable, Eligible and All Treated Patients. Clinical response rates by site were tabulated for the Clinically Evaluable and Eligible Patient populations. Relapse rates among the cured clinically evaluable patients who have extended follow-up was also tabulated. Incidences of new infections among All Treated Patients were compared using a Fisher's Exact Test.

The clinical response rate and clinical response rate by prognostic factor were analyzed for All Treated Patients. In addition, the clinical response rate by study site was tabulated for Clinically Evaluable and Eligible Patients.

The incidences of persistent pathogens were displayed for All Treated Patients, along with the susceptibility of those organisms. The incidence of new infections, the pathogens isolated, if any, and the susceptibility of those pathogens were also tabulated

for All Treated Patients. Pathogens isolated from relapsed patients were displayed for Clinically Evaluable Patients.

*Safety*

All patients who received at least one dose of study medication were evaluated for safety. The frequencies of adverse clinical events were summarized by relationship to study drug and displayed by primary term within the relevant body system, as defined in the COSTART adverse clinical events classification system, which was modified by the applicant. Those adverse events that were considered by the investigator to be drug-related (i.e. certainly, probably or possibly drug-related) were also tabulated by severity. Discontinuations due to adverse events were tabulated. All adverse clinical events and all drug-related adverse events were displayed in appendices.

Changes in laboratory test results were tabulated by test. For patients with normal (Grade 0) pre-treatment laboratory test values, the frequencies of Grade 1, 2, 3, and 4 abnormalities during/post-treatment were displayed. For each patient, the most abnormal result for each test was counted. For patients with abnormal (Grades 1, 2, or 3) pre-treatment laboratory test values, the frequencies of worsening to Grade 2, 3, or 4 abnormalities during/post-treatment were displayed. For each patient, the worst grade change for each test was counted.

## 8.2.2.4 Results

### 8.2.2.4.1 Populations

The study period was from October 6, 1997 to June 15, 1998. A total of 360 patients were enrolled, all in the U.S.; all but two received at least one dose of gatifloxacin or levofloxacin. Four investigators contributed more than half of the total enrollment, while 3 investigators accrued four patients or less. Three hundred thirty-six (93%) patients were Eligible and 296 (82%) patients were Clinically Evaluable. Two hundred and eight patients (58%) were Clinically and Microbiologically Evaluable. The rates of eligibility and evaluability were fairly constant across sites. All patients provided signed informed consent. There were no major protocol violations related to informed consent during the trial.

Significant protocol violations were defined as those that prevented a patient from being clinically evaluable. Fifty-two protocol violations occurred (Table 3). Protocol violations are similar between the gatifloxacin and levofloxacin treatment groups. Five patients received another systemic antibiotic after completion of study drug therapy and before the post-treatment evaluation for an infection other than bronchitis. Four were considered in the "other" category; namely two patients had chest x-rays done outside the window, one patient had the TOC visit outside of the acceptable window, and one patient had an AE which prevented assessment of cardinal symptoms.

Table 3 Significant Protocol Violations, All Enrolled Patients

| | Number of Patients (%) | | | | | |
|---|---|---|---|---|---|---|
| | Gatifloxacin | | Levofloxacin | | Total | |
| Violation | N = 180 | | N = 180 | | N = 360 | |
| No Test of Cure visit | 10 | (6) | 10 | (6) | 20 | (6) |
| No Purulent Sputum Pre-treatment | 9 | (5) | 8 | (4) | 17 | (5) |
| Other Antibiotic Given | 4 | (2) | 1 | (1) | 5 | (1) |
| Other | 4 | (2) | - | | 4 | (1) |
| X-ray evidence of pneumonia pre-treatment | 1 | (1) | 2 | (1) | 3 | (1) |
| Patient did not receive study drug | 1 | (1) | 1 | (1) | 2 | (1) |
| Inadequate Dosage, Lost Meds | - | | 1 | (1) | 1 | (<1) |

No interim analyses were conducted during the study and there were no instances of unblinding. There were no amendments or administrative changes during the study. There were no changes to the protocol or violations sufficient to invalidate the results of the trial.

The reasons for ineligibility were comparable in both the gatifloxacin and levofloxacin arms. Twenty-two of the 358 patients treated were ineligible (Table 4).

Forty Eligible Patients were clinically unevaluable, 22 in gatifloxacin group and 18 in levofloxacin group. The majority (27) were unevaluable because they did not have a post-treatment clinical evaluation within the acceptable window (Day +5 to Day +18, inclusive). Six others were clinically unevaluable because they did not complete the minimum study medication dosing requirement for efficacy evaluation, five received another antibiotic and the remaining two patients were in the other category. The other category consisted of TOC outside of window for one patient and an adverse event prevented assessment of cardinal symptoms for one patient.

One hundred and fifty patients were microbiologically unevaluable; 108 of these had no pre-treatment pathogen. 41 were clinically unevaluable and only one had a resistant pre-treatment pathogen (*S. aureus*).

Table 4 Distribution of Patients in Study Populations and Reasons for Exclusion, All Treated Patients

| Reason | Number of Patients (%) Gatifloxacin N = 179 | | Levofloxacin N = 179 | | Total N = 358 | |
|---|---|---|---|---|---|---|
| **Treated** | **179** | | **179** | | **358** | |
| **Eligible** | **167** | **(93)** | **169** | **(94)** | **336** | **(94)** |
| **Ineligible** | **12** | **(7)** | **10** | **(6)** | **22** | **(6)** |
| Reason Ineligible: | | | | | | |
| No Pre-treatment Purulent Sputum Specimen | 9 | (5) | 8 | (4) | 17 | (5) |
| Evidence of Pneumonia on Pre-treatment X-ray | 1 | (<1) | 2 | (1) | 3 | (<1) |
| Other | 2 | (1) | - | | 2 | (<1) |
| **Clinically Evaluable** | **145** | **(81)** | **151** | **(84)** | **296** | **(83)** |
| **Clinically Unevaluable** | **34** | **(19)** | **28** | **(16)** | **62** | **(17)** |
| Reason Unevaluable: | | | | | | |
| No Test of Cure visit | 14 | (8) | 13 | (7) | 27 | (8) |
| Ineligible | 12 | (7) | 10 | (6) | 22 | (6) |
| Insufficient Dosage | 2 | (1) | 4 | (2) | 6 | (2) |
| Other Antibiotic Received | 4 | (2) | 1 | (<1) | 5 | (1) |
| Other | 2 | (1) | - | | 2 | (<1) |
| **Microbiologically Evaluable** | **107** | **(60)** | **101** | **(56)** | **208** | **(58)** |
| **Microbiologically Unevaluable** | **72** | **(40)** | **78** | **(44)** | **150** | **(42)** |
| Reason Unevaluable: | | | | | | |
| Clinically Unevaluable | 25 | (14) | 16 | (9) | 41 | (11) |
| No Pre-treatment Pathogen | 46 | (26) | 62 | (35) | 108 | (30) |
| Resistant Pathogen | 1 | (<1) | - | | 1 | (<1) |

***Reviewer's comments:*** *Patients were well balanced between the 2 groups in terms of eligibility, clinical evaluability and microbiological evaluability. They were also well balanced in terms of reasons for ineligibility and unevaluability. Reviewer agrees with applicant regarding the ineligibility of 22 patients whose sputum was not purulent (17 patients), who had evidence of pneumonia on the chest X-ray (3 patients) or did not receive study drug (2 patients). These facts were well documented on the case repor:*

*forms and in the databases. Reviewer also agrees regarding the unevaluability of 62 patients via the case report forms and the databases.*

***Data Sets***

The safety data set consisted of All Treated Patients.
The primary data set for analysis of clinical efficacy consisted of the Clinically Evaluable Patients; the primary data set for analysis of bacteriologic efficacy consisted of the Microbiologically Evaluable Patients. The Eligible and All Treated Patients formed secondary efficacy data sets.

***Demography and Patient Characteristics***

Of the 358 patients treated, 59% were male; the majority was white and the median age was 49 years (Table 5). There were more males in the levofloxacin-treated group; otherwise, demographics in the gatifloxacin treated patients were similar to the levofloxacin-treated patients.



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Table 5 Demography, All Treated Patients

| Characteristic | Gatifloxacin N = 179 | | Levofloxacin N = 179 | | Total N = 358 | |
|---|---|---|---|---|---|---|
| Gender [N (%)]: | | | | | | |
| Male | 95 | (53) | 116 | (65) | 211 | (59) |
| Female | 84 | (47) | 63 | (35) | 147 | (41) |
| Race:[N(%)] | | | | | | |
| White | 130 | (73) | 126 | (70) | 256 | (72) |
| Black | 43 | (24) | 47 | (26) | 90 | (25) |
| Hispanic | 5 | (3) | 6 | (3) | 11 | (3) |
| Other | 1 | (<1) | - | | 1 | (<1) |
| Age (years): | | | | | | |
| Mean | 51 | | 51 | | 51 | |
| Median | 49.0 | | 50.0 | | 49.0 | |
| Min – Max | 19 – 85 | | 18 - 83 | | 18 - 85 | |
| Weight (kg): | | | | | | |
| Mean | 79.2 | | 81.1 | | 80.2 | |
| Median | 77.1 | | 78.5 | | 77.6 | |
| Min - Max | 37.6 – 145.1 | | 37.6 – 154.4 | | 37.6 – 154.4 | |

***Reviewer's comments:*** *It is unlikely that the imbalance in gender representation between the two groups will affect study results given the nature of the disease.*

***Medical History and Presenting Conditions***

A wide variety of medical conditions was recorded. One hundred percent of the patients had a history of any respiratory condition; all had chronic bronchitis, in meeting the definition of chronic cough and sputum production on most days for 3 consecutive months for greater than two consecutive years.

The number of episodes of AECB that the patients had experienced in the previous 12 months was similar between the two treatment groups; the majority (67%) had had 2 or 3 episodes during the previous year.

At the time of enrollment, one patient on levofloxacin was being treated with an antibacterial cefotaxime, for acute exacerbation of chronic bronchitis. One patient in each arm received acyclovir, one for herpes simplex virus and one for genital herpes. Pre-treatment systemic corticosteroid use was infrequent but similar between groups.

Based on signs of bronchitis present at entry almost all patients on the gatifloxacin and levofloxacin arm had increased sputum production and increased sputum purulence. The two treatment groups were identical for pre-treatment cough and dyspnea.
The majority of patients presented with additional signs and symptoms associated with acute exacerbation of chronic bronchitis. There were no appreciable differences between the treatment groups. Most had auscultatory findings consistent with bronchial disease (i.e., wheezing, rhonchi, and rales). Other relevant symptoms included tightness in the chest, malaise and sinus congestion.

***Reviewer's comments:*** *The representation of different medical conditions was adequate, well balanced between the 2 groups, and reflected the picture encountered in clinical practice.*

***Microbiologic Documentation***

A total of 334 pathogens were isolated from 250 (70%) patients. One hundred seventy-three patients had a single pathogen and 77 had multiple pathogens. There were 57 isolates of *H. influenzae*, 37 of *S. pneumoniae*, and 74 of *M. catarrhalis*. Generally, each treatment group had similar numbers of each pathogen. Of the *H. influenzae* isolates, there were 13 β-lactamase positive in each treatment arm. There were 3 gatifloxacin and two levofloxacin patients with penicillin resistant (>1.0 μg/mL) *S. pneumoniae*. Other frequently isolated respiratory organisms included *S. aureus* (59) and *H. parainfluenzae* (46). *Pseudomonas aeruginosa* was isolated from the pre-treatment sputum of one patient randomized to gatifloxacin and six randomized to levofloxacin. One pre-treatment pathogen was resistant to both gatifloxacin and levofloxacin and one to levofloxacin only.

***Reviewer's comments:*** *The 3 major pathogens usually involved in AECB (H. influenzae, S. pneumoniae and M. catarrhalis) are well represented in the study. There was also a good proportion of patients with H. parainfluenzae and S. aureus to allow for assessment of efficacy against those organisms.*

***Prognostic Factors, All Treated Patients***

Most (86%) patients had Type I exacerbation by Anthonisen, one gatifloxacin patient was a Type III exacerbation manifested by increased sputum production and cough, and the remainder had Type II . The median duration of the current episode of exacerbation prior to enrollment was six days, for both gatifloxacin and levofloxacin arms, and in 80% of the patients the current episode was less than fifteen days in duration. Twenty-eight patients received pre-treatment systemic corticosteroids with similar frequency in both arms. Fifty-nine percent of the total patients were smokers or had stopped smoking within the two months before enrollment, and 87% had a history of smoking, with the two arms being similar. Prognostic factors were also comparable among the Clinically Evaluable patients.

***Reviewer's comments:*** *The two groups were generally similar in terms of exacerbation type, smoking history, current smoking status, duration of current episode of AECB, and pre-treatment systemic corticosteroid use.*

*Study Therapy*

The majority of the patients received 7 to 10 days (doses) of therapy in both treatment groups. Duration of less than 7 days occurred in 11 (6%) gatifloxacin patients and 9 (5%) of the levofloxacin patients. A total of 23 (6%) patients discontinued gatifloxacin and levofloxacin treatment prematurely. There were no interruptions of therapy related to clinical findings or laboratory abnormalities that occurred on therapy. There were 3 patients on levofloxacin who took 11 days to take the 10 day regimen because they forgot to take their dose on either Day 10 (two patients) or Day 7 (one patient). The mean and median duration of therapy was 9 and 10 days, respectively, for both groups.

*Concomitant Therapy*

No patient in either the gatifloxacin or the levofloxacin arm received systemic concomitant antibacterial. Systemic antivirals were a continuation of prior therapy. The remaining medications were topical agents. Corticosteroid use was equally distributed between the treatment groups. Thirty-three patients received a systemic corticosteroid.

*Post-treatment Therapy*

The 50 patients who received systemic antibacterial agents post-treatment (31 gatifloxacin patients, 19 levofloxacin patients) fell into four main groups:

- Treatment failures who received an alternate antibiotic for AECB: 12 gatifloxacin patients, 6 levofloxacin patients;
- Patients who were treated for new infections: 9 gatifloxacin patients, 4 levofloxacin patients;
- Patients who discontinued study therapy prematurely due to an adverse event: 3 gatifloxacin patients, 3 levofloxacin patients;
- Patients who were cured at TOC visit and relapsed: 7 gatifloxacin patients, 6 levofloxacin patients.

<u>5.2.2.4.2 Efficacy Results</u>

***Reviewer's comments:***

*1) Although patients were randomized according to smoking status, confidence intervals were constructed only for the group as a whole.*

*2) The primary efficacy analysis was not done on an intent-to-treat basis; patients who discontinued study drug before receiving 5 days of therapy because of adverse events or worsening of their condition were not considered evaluable and thus were not included in the primary efficacy analysis. These patients were well balanced between the two study*

*groups. The intent-to-treat population would be more closely represented by the All Treated or the Eligible subsets. Analyses of all subsets will be considered by the FDA.*
*3) The applicant's definition of cure included those patients whose symptoms improved as well as those whose symptoms returned to baseline. This definition without a grading system for improvement and a separate analysis for this subset of patients makes the interpretation of the trial's data difficult. For this reason a separate analysis was done that considered as cured only those patients whose 3 cardinal symptoms of cough, dyspnea and sputum production either returned to baseline at the TOC visit, or were only improved at the TOC visit but returned to baseline at the extended follow-up visit. Thus, an additional 25 patients in gatifloxacin group (11 smokers, 14 non-smokers) and an additional 26 patients in levofloxacin group (10 smokers and 16 non-smokers) were considered as failures. This was referred to as "reviewer's analysis #1".*
*4) Another separate analysis was done that considered ineligible those patients whose sputum contained >10 epithelial cells/LPF, since relaxation of this criterion was done at the end of the study. There were 15 such patients (13 of whom were evaluable) in gatifloxacin group (11 smokers, 4 non-smokers) and 20 patients (19 of whom were evaluable) in levofloxacin group (14 smokers, 6 non-smokers). This was referred to as "reviewer's analysis #2".*
*5) A third analysis was done that took into account both above issues. This was referred to as "reviewer's analysis #3".*

## Clinically Evaluable Patients

Cure rates were similar in the two treatment groups per the applicant's analysis (gatifloxacin = 88%, levofloxacin = 92%), 95% CI (-14.6%, 6.2%) (Table 6).

Table 6 Clinical Response, Clinically Evaluable Patients

| | Gatifloxacin | | Levofloxacin | | Total | | CI[a] |
|---|---|---|---|---|---|---|---|
| Clinical Response | Number of Patients (%) | | | | | | |
| **Applicant's Analysis** | | | | | | | |
| | N = 145 | | N = 151 | | N = 296 | | -14.6%, 6.2% |
| Cure | 127 | (88) | 139 | (92) | 266 | (90) | |
| Failure | 18 | (12) | 12 | (8) | 30 | (10) | |
| **Reviewer's Analysis #1** | | | | | | | |
| | N = 145 | | N = 151 | | N = 296 | | -13.8%, 5.6% |
| Cure | 102 | (70) | 113 | (75) | 215 | (73) | |
| Failure | 43 | (30) | 38 | (25) | 81 | (27) | |
| **Reviewer's Analysis #2** | | | | | | | |
| | N = 132 | | N = 132 | | N = 264 | | -16.3%, 9.1% |
| Cure | 115 | (87) | 120 | (91) | 235 | (89) | |
| Failure | 17 | (13) | 12 | (9) | 29 | (11) | |
| **Reviewer's Analysis #3** | | | | | | | |
| | N = 132 | | N = 132 | | N = 264 | | -15.7%, 8.4% |
| Cure | 94 | (71) | 99 | (75) | 193 | (73) | |
| Failure | 38 | (29) | 33 | (25) | 71 | (27) | |

[a] 95% Confidence Interval for the difference in Cure Rate

*Reviewer's comments: Cure rates were slightly higher for levofloxacin across all analyses. The lower limit of the 95% CI for the 4 analyses is within or slightly beyond the designated limit of –15%.*

***Clinical Response by Duration of Therapy***

Seven-day therapy of AECB was as effective as 10 days for both gatifloxacin and levofloxacin (Table 7).

Table 7 Clinical Response by Duration of Therapy, Clinically Evaluable Patients

| | Number Cured/Evaluable Patients (%) | | | | | |
|---|---|---|---|---|---|---|
| Duration of Dosing (Days) | Gatifloxacin N = 145 | | Levofloxacin N = 151 | | Total N = 296 | |
| 7 | 42/42 | (100) | 42/42 | (100) | 84/84 | (100) |
| 10 | 85/100 | (85) | 92/103 | (89) | 177/203 | (87) |

Note: No patients received 8 or 9 days of gatifloxacin.

***Clinical Response by Prognostic Factor***

The clinical response rate of cure for Clinically Evaluable Patients was generally similar across the categories of potential prognostic relevance for both drugs (Table 8). Among current smokers equal response rates (94%) were observed.

Table 8 Clinical Cure Rates by Prognostic Factor, Clinically Evaluable Patients

| Prognostic Factor/ Subcategory | Number Cured/Evaluable Patients (%) Gatifloxacin N = 145 | | Levofloxacin N = 151 | | Total N = 296 | |
|---|---|---|---|---|---|---|
| Exacerbation Type | | | | | | |
| Type I | 112/127 | (88) | 122/132 | (92) | 234/259 | (90) |
| Type II | 15/17 | (88) | 17/19 | (89) | 32/36 | (89) |
| Duration of Current Episode | | | | | | |
| 0 - 7 Days | 76/83 | (92) | 86/91 | (95) | 162/174 | (93) |
| >7 Days | 49/60 | (82) | 50/57 | (88) | 99/117 | (85) |
| Not Recorded | 2/2 | (100) | 3/3 | (100) | 5/5 | (100) |
| Pre-treatment Systemic Corticosteroid Use | | | | | | |
| Yes | 8/10 | (80) | 12/14 | (86) | 20/24 | (83) |
| No | 119/135 | (88) | 127/137 | (93) | 246/272 | (90) |
| Current Smoking Status | | | | | | |
| Smoker | 78/83 | (94) | 77/82 | (94) | 155/165 | (94) |
| Non-Smoker | 49/62 | (79) | 62/69 | (90) | 111/131 | (85) |
| History of Smoking | | | | | | |
| Yes | 111/124 | (90) | 123/135 | (91) | 234/259 | (90) |
| No | 16/21 | (76) | 16/16 | (100) | 32/37 | (86) |

***Reviewer's comments:*** *There was a higher response rate seen in current smokers compared to non-smokers in both treatment arms. A separate analysis that examined the difference in cure rates between the 2 drugs according to current smoking status is presented below (Table 9). It shows that the 2 drugs had similar cure rates in current smokers and that levofloxacin had a higher cure rate in non-smokers. Since this could be due to a potential imbalance in other patient characteristics, a closer look at the distribution of smokers and non-smokers with respect to age, race, gender, history of asthma, use of other drugs concomitantly (corticosteroids, Beta adrenergics and anticholinergics) and the presence of one of the 5 major pathogens isolated, was performed retrospectively by the applicant at the reviewer's request and identified a number of differences between the 2 subsets. The most notable differences were in race (90% of non-smokers being white vs. 57% for smokers), age (mean age of 61 for non-smokers vs. 44 for smokers), history of asthma (32% for non-smokers vs. 16% for smokers) and concomitant use of respiratory drugs (63% for non-smokers vs. 24% for*

*smokers). Logistic regression analyses on the clinical response were also performed retrospectively by the applicant for current smoking status and history of smoking using the following covariates: age, race, gender, history of asthma, use of other drugs concomitantly and the presence of one of the 5 major pathogens isolated. Various adjustments for these characteristics minimized the impact of smoking in most analyses. Race and history of asthma were the only independent prognostic variables identified, with non-Whites and those without a history of asthma having higher cure rates.*

Table 9 Clinical Response by Smoking Status, Clinically Evaluable Patients

| | Gatifloxacin | | Levofloxacin | | Total | | CI[a] |
|---|---|---|---|---|---|---|---|
| Clinical Response | Number of Patients (%) | | | | | | |
| **Applicant's Analysis** | | | | | | | |
| | N = 145 | | N = 151 | | N = 296 | | S(-10.9%,11.2%) |
| | S=83 | NS=62 | S=82 | NS=69 | S=165 | NS=131 | |
| Cure | 78 (94) | 49 (79) | 77 (94) | 62 (90) | 155 | 111 | NS(-27.3%,4.1%) |
| Failure | 5 | 13 | 5 | 7 | 10 | 20 | |
| **Reviewer's Analysis #1[b]** | | | | | | | |
| | N = 145 | | N = 151 | | N = 296 | | S(-16.3%,12.4%) |
| | S=83 | NS=62 | S=82 | NS=69 | S=165 | NS=131 | |
| Cure | 67 (80) | 35 (56) | 67 (82) | 46 (67) | 134 | 81 | NS(-28.4%,7.1%) |
| Failure | 16 | 27 | 15 | 23 | 31 | 50 | |
| **Reviewer's Analysis #2[b]** | | | | | | | |
| | N = 132 | | N = 132 | | N = 264 | | S(-9.8%,14.7%) |
| | S=74 | NS=58 | S=69 | NS=63 | S=143 | NS=121 | |
| Cure | 70 (94) | 45 (78) | 64 (93) | 56 (89) | 134 | 101 | NS(-28.7%,4.6%) |
| Failure | 4 | 13 | 5 | 7 | 9 | 20 | |
| **Reviewer's Analysis #3[b]** | | | | | | | |
| | N = 132 | | N = 132 | | N = 264 | | S(-13.4%,17.1%) |
| | S=74 | NS=58 | S=69 | NS=63 | S=143 | NS=121 | |
| Cure | 62 (84) | 32 (55) | 57 (83) | 42 (67) | 119 | 74 | NS(-30.5%,6.6%) |
| Failure | 12 | 26 | 12 | 21 | 24 | 47 | |

[a] 95% Confidence Interval for the difference in Cure Rates by smoking status (S= Current smokers; NS= Non-smokers)

[b] For the description of the reviewer's analyses, refer to section 8.2.2.4.2 (Efficacy Results)

*Clinical Cure Rates by Pathogen*

Clinical responses by pathogen were generally similar between the two treatment groups (Table 10). The cure rate for patients with a pathogen was 88% and 92% for gatifloxacin and levofloxacin, respectively (95% CI, - 10.6, 3.3). The cure rate by pathogen for gatifloxacin was 87% and 91% for levofloxacin.

There were 3 *S. pneumoniae* treatment failures in the gatifloxacin arm. They all failed clinically at least 7 days after completion of therapy due to persistence or worsening of primary signs or symptoms. In those clinical failures *S. pneumoniae* was eradicated at the TOC visit.

Table 10 Clinical Cure Rates by Pathogen, Clinically Evaluable Patients

| | Number Cured/Number Isolated (%) | | | | | |
|---|---|---|---|---|---|---|
| Pathogen[a]/Subtype | Gatifloxacin | | Levofloxacin | | Total | |
| Total patients with pathogens[b] | 95/108 | (88) | 93/101 | (92) | 188/209 | (90) |
| Total pathogens | 123/142 | (87) | 125/138 | (91) | 248/280 | (89) |
| *H. influenzae* | 24/26 | (92) | 20/21 | (95) | 44/47 | (94) |
| β-Lactamase - | 12/14 | (86) | 10/11 | (91) | 22/25 | (88) |
| β-Lactamase + | 11/11 | (100) | 9/9 | (100) | 20/20 | (100) |
| β-Lactamase Unknown | 1/1 | (100) | 1/1 | (100) | 2/2 | (100) |
| *M. catarrhalis* | 32/36 | (89) | 23/27 | (85) | 55/63 | (87) |
| β-Lactamase - | 3/3 | (100) | 4/4 | (100) | 7/7 | (100) |
| β-Lactamase + | 28/32 | (88) | 19/23 | (83) | 47/55 | (85) |
| β-Lactamase Unknown | 1/1 | (100) | - | | 1/1 | (100) |
| *H. parainfluenzae* | 12/15 | (80) | 19/22 | (86) | 31/37 | (84) |
| β-Lactamase - | 10/12 | (83) | 17/19 | (89) | 27/31 | (87) |
| β-Lactamase + | 1/2 | (50) | 2/3 | (67) | 3/5 | (60) |
| β-Lactamase Unknown | 1/1 | (100) | - | | 1/1 | (100) |
| *S. pneumoniae* | 10/13 | (77) | 16/17 | (94) | 26/30 | (87) |
| Penicillin Sensitive | 6/8 | (75) | 9/9 | (100) | 15/17 | (88) |
| Penicillin Intermediate | 3/4 | (75) | 5/6 | (83) | 8/10 | (80) |
| Penicillin Resistant | 1/1 | (100) | 2/2 | (100) | 3/3 | (100) |
| *S. aureus* | 22/27 | (81) | 24/25 | (96) | 46/52 | (88) |
| *K. pneumoniae* | 1/1 | (100) | 2/2 | (100) | 3/3 | (100) |
| *P. aeruginosa* | 1/1 | (100) | 4/6 | (67) | 5/7 | (71) |
| *E. cloacae* | 2/3 | (67) | 1/1 | (100) | 3/4 | (75) |
| Other Gram-negative[c] | 6/7 | (86) | 4/4 | (100) | 10/11 | (91) |
| Other Gram-positive[d] | 13/13 | (100) | 12/12 | (100) | 25/25 | (100) |

a A patient may have had more than one pathogen isolated pre-treatment
b 95% CI, -10.6, 3.3.
c Consisted of 7 organisms.
d Consisted of 4 organisms.

***Reviewer's comments:*** *Reviewer agrees with the data presented in this table via the databases. Cure rates were comparable for the 5 pathogens isolated most commonly. The confidence interval for the difference in cure rates of those patients with a pathogen was acceptable (–10.6 to 3.3).*

*Relapses*

Of the patients who were cured initially, the sustained cure rates of 94% and 95% for gatifloxacin and levofloxacin were similar (Table 11). Fifteen patients with a clinical response of cured at the TOC visit relapsed with AECB at the extended follow-up visit, Day +21 to +28. There were 3 relapses in gatifloxacin patients receiving 7 days of treatment and 5 in those receiving 10 days of gatifloxacin.

Table 11 Clinical Assessment at Extended Follow-up, Clinically Evaluable Patients

| | Numbers of Patients (%) | | | | | |
|---|---|---|---|---|---|---|
| | Gatifloxacin N = 145 | | Levofloxacin N = 151 | | Total N = 296 | |
| Cured at Test of Cure visit | 127 | (88) | 139 | (92) | 266 | (90) |
| Late Follow-Up Obtained | 127 | | 139 | | 266 | |
| Sustained Cure | 119 | (94) | 132 | (95) | 251 | (94) |
| Relapse | 8 | (6) | 7 | (5) | 15 | (6) |
| ***Reviewer's analysis (Relapse)*** | **6** | **(4)** | **8** | **(5)** | **14** | **(5)** |

***Reviewer's comments:*** *The reviewer's analysis shows that there were 6 and 8 relapses in gatifloxacin and levofloxacin groups, respectively.*

## Micobiologically Evaluable Patients

*Clinical Cure Rates by Pathogen*

The cure rate for patients with a pathogen was 88% for those treated with gatifloxacin and 92% for levofloxacin treated patients in the Microbiologically Evaluable population (95% CI, -10.7, 3.3).

Clinical response by pathogen was similar across the treatment groups with gatifloxacin achieving an 87% cure rate and levofloxacin a 91% cure rate. The one patient who had a pre-treatment pathogen resistant to gatifloxacin received levofloxacin.

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Table 12 Clinical Cure Rates Response by Pathogen, Microbiologically Evaluable Patients

| | Number Cured/All Pathogens % | | | | | |
|---|---|---|---|---|---|---|
| Pathogen[a] | Gatifloxacin | | Levofloxacin | | Total | |
| Total patients with pathogen[b] | 94/107 | (88) | 93/101 | (92) | 187/208 | (90) |
| Total pathogens | 122/141 | (87) | 125/137 | (91) | 247/278 | (89) |
| *H. influenzae* | 24/26 | (92) | 20/21 | (95) | 44/47 | (94) |
| β-lactamase + | 11/11 | (100) | 9/9 | (100) | 20/20 | (100) |
| β-lactamase - | 12/14 | (86) | 10/11 | (91) | 22/25 | (88) |
| β-lactamase Unknown | 1/1 | (100) | 1/1 | (100) | 2/2 | (100) |
| *M. catarrhalis* | 32/36 | (89) | 23/27 | (85) | 55/63 | (87) |
| β-lactamase + | 28/32 | (88) | 19/23 | (83) | 47/55 | (85) |
| β-lactamase - | 3/3 | (100) | 4/4 | (100) | 7/7 | (100) |
| β-lactamase Unknown | 1/1 | (100) | - | | 1/1 | (100) |
| *H. parainfluenzae* | 12/15 | (80) | 19/22 | (86) | 31/37 | (84) |
| β-lactamase + | 1/2 | (50) | 2/3 | (67) | 3/5 | (60) |
| β-lactamase - | 10/12 | (83) | 17/19 | (89) | 27/31 | (87) |
| β-lactamase Unknown | 1/1 | (100) | - | | 1/1 | (100) |
| *S. pneumoniae* | 10/13 | (77) | 16/17 | (94) | 26/30 | (87) |
| Penicillin Susceptible | 6/8 | (75) | 9/9 | (100) | 15/17 | (88) |
| Penicillin Intermediate | 3/4 | (75) | 5/6 | (83) | 8/10 | (80) |
| Penicillin Resistant | 1/1 | (100) | 2/2 | (100) | 3/3 | (100) |
| *S. aureus* | 21/26 | (81) | 24/25 | (96) | 45/51 | (88) |
| *K. pneumoniae* | 1/1 | (100) | 2/2 | (100) | 3/3 | (100) |
| *P. aeruginosa* | 1/1 | (100) | 4/5 | (80) | 5/6 | (83) |
| *E. cloacae* | 2/3 | (67) | 1/1 | (100) | 3/4 | (75) |
| Other Gram-positive | 13/13 | (100) | 12/12 | (100) | 25/25 | (100) |
| Other Gram-negative | 6/7 | (86) | 4/5 | (80) | 10/12 | (83) |

a A patient may have had more than one pathogen isolated.
b 95% CI, -10.7, 3.3.

***Reviewer's comments:*** *There were adequate numbers of patients harboring H. influenzae, M. catarrhalis, S. pneumoniae, H. parainfluenzae or S. aureus for assessment of efficacy. These data show effectiveness of gatifloxacin against these organisms, even after a separate analysis was done excluding patients with >10 epithelial cells/LPF and adjusting for the definition of cure. There were insufficient data to show effectiveness*

*against penicillin-intermediate and penicillin-resistant S. pneumoniae. A review of patients with the latter organisms reveals that none of the 4 gatifloxacin patients who harbored these organisms and were clinically cured had a sputum culture done post-treatment, i.e. they were all in the presumed eradicated category. One such patient in levofloxacin group was in the eradicated category.*

***Bacteriologic Response***

Bacteriologic eradication rates were similar across the treatment groups (Table 13). The total eradication rate of all pathogens was the same, 94% for both gatifloxacin and levofloxacin. In the great majority of cases, pathogen eradication was presumed (i.e., based on the clinical response).

Table 13 Bacteriologic Eradication Rates by Pathogen, Microbiologically Evaluable Patients

| | Number Eradicated/Number Isolated (%) | | | | | |
|---|---|---|---|---|---|---|
| Pathogen | Gatifloxacin | | Levofloxacin | | Total | |
| Total | 132/141 | (94) | 129/137 | (94) | 261/278 | (94) |
| *H. influenzae* | 26/26 | (100) | 21/21 | (100) | 47/47 | (100) |
| β-Lactamase + | 11/11 | (100) | 9/9 | (100) | 20/20 | (100) |
| β-Lactamase - | 14/14 | (100) | 11/11 | (100) | 25/25 | (100) |
| β-Lactamase Unknown | 1/1 | (100) | 1/1 | (100) | 2/2 | (100) |
| *M. catarrhalis* | 34/36 | (94) | 24/27 | (89) | 58/63 | (92) |
| β-Lactamase + | 30/32 | (94) | 20/23 | (87) | 50/55 | (91) |
| β-Lactamase - | 3/3 | (100) | 4/4 | (100) | 7/7 | (100) |
| β-Lactamase Unknown | 1/1 | (100) | - | | 1/1 | (100) |
| *H. parainfluenzae* | 13/15 | (87) | 21/22 | (95) | 34/37 | (92) |
| β-Lactamase + | 2/2 | (100) | 2/3 | (67) | 4/5 | (80) |
| β-Lactamase - | 10/12 | (83) | 19/19 | (100) | 29/31 | (94) |
| β-Lactamase Unknown | 1/1 | (100) | - | | 1/1 | (100) |
| *S. pneumoniae* | 13/13 | (100) | 15/17 | (88) | 28/30 | (93) |
| Penicillin Susceptible | 8/8 | (100) | 9/9 | (100) | 17/17 | (100) |
| Penicillin Intermediate | 4/4 | (100) | 4/6 | (67) | 8/10 | (80) |
| Penicillin Resistant | 1/1 | (100) | 2/2 | (100) | 3/3 | (100) |
| *S. aureus* | 22/26 | (85) | 24/25 | (96) | 46/51 | (90) |
| *K. pneumoniae* | 1/1 | (100) | 2/2 | (100) | 3/3 | (100) |
| *P. aeruginosa* | 1/1 | (100) | 5/5 | (100) | 6/6 | (100) |
| *E. cloacae* | 2/3 | (67) | 1/1 | (100) | 3/4 | (75) |
| Others[a] | | | | | | |
| Gram-positive | 13/13 | (100) | 12/12 | (100) | 25/25 | (100) |
| Gram-negative | 7/7 | (100) | 4/5 | (80) | 11/12 | (92) |

[a] A patient may have had more than one pathogen isolated.

Indication: Acute Exacerbations of Chronic Bronchitis

Table 14: Bacteriologic Eradication Rates by Pathogen, Microbiologically Evaluable Patients **(Reviewer's analysis)**

| Pathogen | Number Eradicated/Number Isolated (%) | | | |
|---|---|---|---|---|
| | Gatifloxacin | | Levofloxacin | |
| *H. influenzae* | 21/25 | (84) | 18/19 | (95) |
| *M. catarrhalis* | 29/33 | (88) | 20/26 | (77) |
| *H. parainfluenzae* | 10/13 | (77) | 13/19 | (68) |
| *S. pneumoniae* | 12/13 | (92) | 14/16 | (87) |
| *S. aureus* | 14/21 | (66) | 18/20 | (90) |

***Reviewer's comments:*** *The applicant's data above (Table 13) and the reviewer's analysis of the data (Table 14) show efficacy over the 5 most frequently isolated pathogens. The reviewer's analysis excluded patients with >10 epithelial cells/LPF as ineligible, and for those patients whose outcome was changed from cure to failure (see above "Efficacy Results"), a bacteriologic outcome of "presumed eradicated" was changed to "presumed persisted". A review of patients with penicillin-intermediate S. pneumoniae reveals that only one of the 4 gatifloxacin patients who harbored these organisms and had a bacteriological eradication had a sputum culture done post-treatment, i.e. 3 patients were in the presumed eradicated category and one in the eradicated category. The same is true for levofloxacin. No patients with penicillin-resistant S. pneumoniae were in the eradicated category. Since the role of S. aureus in AECB is not entirely clear, a closer look at patients with this organism showed that only 8 patients had a pure growth of S. aureus, 5 of which had a presumed bacteriological eradication and one a confirmed eradication.*

## Eligible Patients

*Clinical Efficacy*

Eighty percent of the Eligible Patients had a clinical response of Cure per the applicant's analysis (Table 15), 77% for gatifloxacin vs. 83% for levofloxacin.

Table 15 Clinical Response, Eligible Patients

| | Gatifloxacin | | Levofloxacin | | Total | | CI[a] |
|---|---|---|---|---|---|---|---|
| Clinical Response | Number of Patients (%) | | | | | | |
| **Applicant's Analysis** | | | | | | | |
| | N = 167 | | N = 169 | | N = 336 | | |
| Cure | 129 | (77) | 141 | (83) | 270 | (80) | -17.6%, 4.5% |
| Failure | 18 | (11) | 12 | (7) | 30 | (9) | |
| Unable to Determine | 20 | (12) | 16 | (9) | 36 | (11) | |
| **Reviewer's Analysis #1[b]** | | | | | | | |
| | N = 167 | | N = 169 | | N = 336 | | |
| Cure | 103 | (62) | 114 | (68) | 217 | (65) | -15.9%, 4.3% |
| Failure | 44 | (26) | 39 | (23) | 83 | (24) | |
| Unable to Determine | 20 | (12) | 16 | (9) | 36 | (11) | |
| **Reviewer's Analysis #2[b]** | | | | | | | |
| | N = 152 | | N = 149 | | N = 301 | | |
| Cure | 117 | (77) | 122 | (82) | 239 | (80) | -19.8%, 8.8% |
| Failure | 17 | (11) | 12 | (8) | 29 | (9) | |
| Unable to Determine | 18 | (12) | 15 | (10) | 33 | (11) | |
| **Reviewer's Analysis #3[b]** | | | | | | | |
| | N = 152 | | N = 149 | | N = 301 | | |
| Cure | 95 | (63) | 100 | (67) | 195 | (65) | -18.1%, 8.2% |
| Failure | 39 | (25) | 34 | (23) | 73 | (24) | |
| Unable to Determine | 18 | (12) | 15 | (10) | 33 | (11) | |

[a] 95% Confidence Interval for the difference in Cure Rate

[b] For the description of the reviewer's analyses, refer to section 8.2.2.4.2 (Efficacy Results)

***Reviewer's comments:*** *Cure rates were higher for levofloxacin among the clinically eligible patients in all 4 analyses, with lower limits for the 95% CI exceeding 15%. A separate analysis that examined the difference in cure rates between the 2 drugs according to current smoking status is presented below (Table 16). Again, levofloxacin had a higher cure rate in non-smokers.*